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Levine et al.

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(54) **BIOADHESIVE PROGRESSIVE HYDRATION TABLETS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 946 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/431,611**

(22) Filed: **May 11, 2006**

(65) **Prior Publication Data**

US 2007/0031491 A1 Feb. 8, 2007

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/421,840, filed on Apr. 24, 2003, now Pat. No. 7,153,845, and a continuation-in-part of application No. 09/877,218, filed on Jun. 11, 2001, now Pat. No. 6,624,200, which is a continuation-in-part of application No. 09/596,073, filed on Jun. 16, 2000, now abandoned, which is a continuation-in-part of application No. 09/379,310, filed on Aug. 23, 1999, now Pat. No. 6,248,358.

(60) Provisional application No. 60/376,545, filed on May 1, 2002, provisional application No. 60/097,843, filed on Aug. 25, 1998.

(51) **Int. Cl.**

A61K 9/22	(2006.01)
A61K 31/33	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/006*** (2013.01); ***A61K 9/0031*** (2013.01); ***A61K 9/0034*** (2013.01)

USPC **424/468**; 514/183

(58) **Field of Classification Search**

None

See application file for complete search history.

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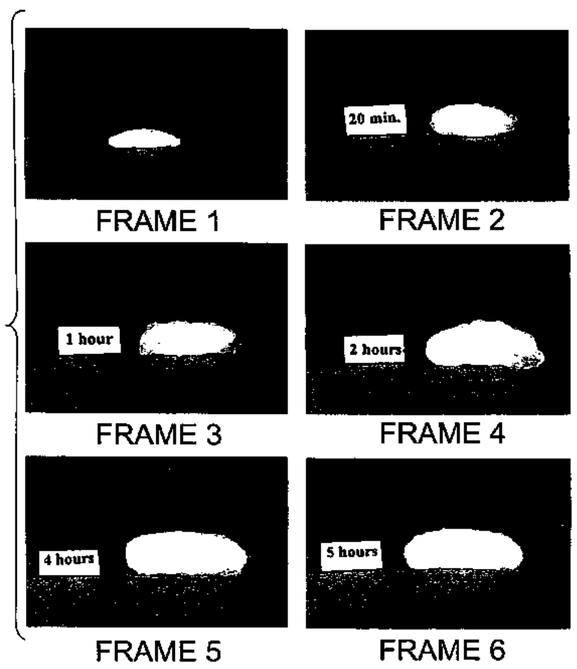
(57) **ABSTRACT**

A bioadhesive controlled, extended release progressive hydration composition wherein the active ingredient may be protected from water or the surrounding environment, thereby protecting it from metabolism or from other degradation caused by moisture, enzymes, or pH effects, and making it bioavailable only at a controlled rate. The active ingredient may be protected from moisture during the manufacturing process, as necessary or desired, and more importantly may be protected from moisture and the immediate septic environment until well after the patient has applied the composition, and then only at a slow and controlled rate. It is by this process of progressive hydration that the active ingredient remains protected for many hours after administration. It is also by the process of progressive hydration that controlled and sustained release is achieved because only that part of the active ingredient that is the hydrated (aqueous) fraction of the composition is available for absorption (bioavailable).

29 Claims, 6 Drawing Sheets



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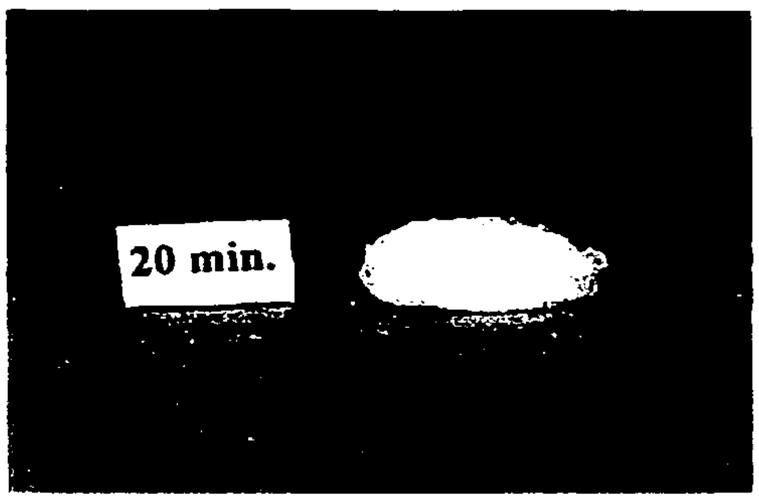

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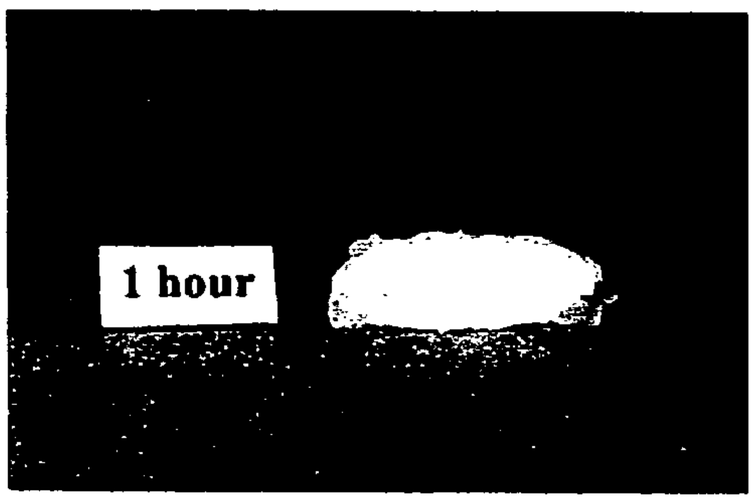

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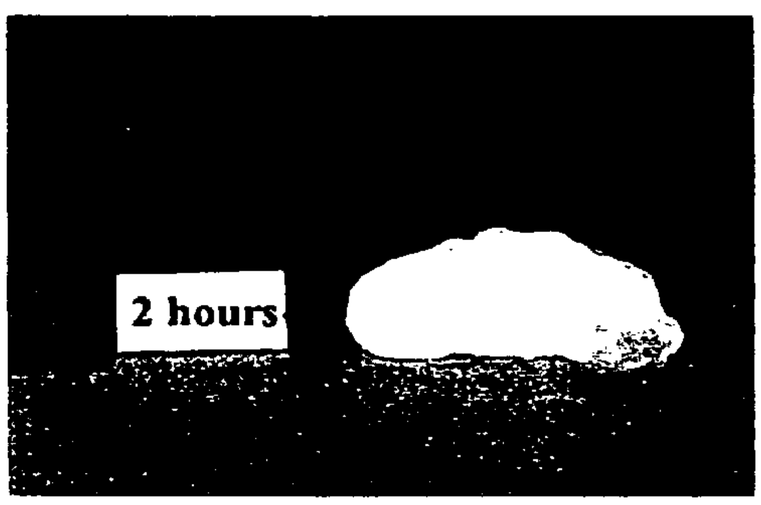

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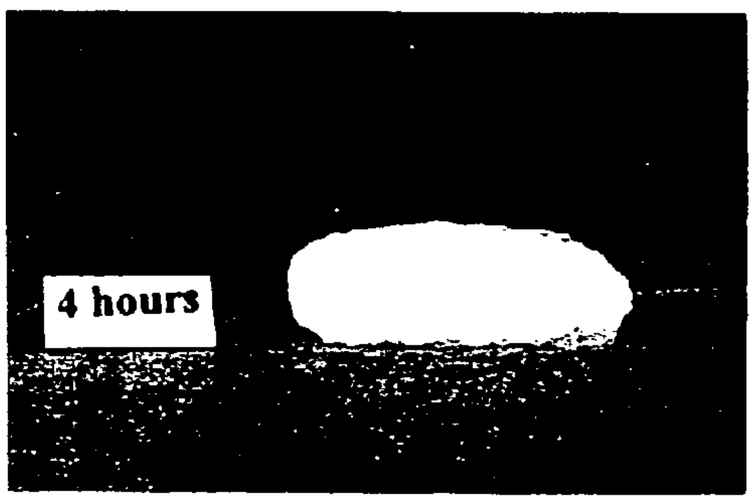

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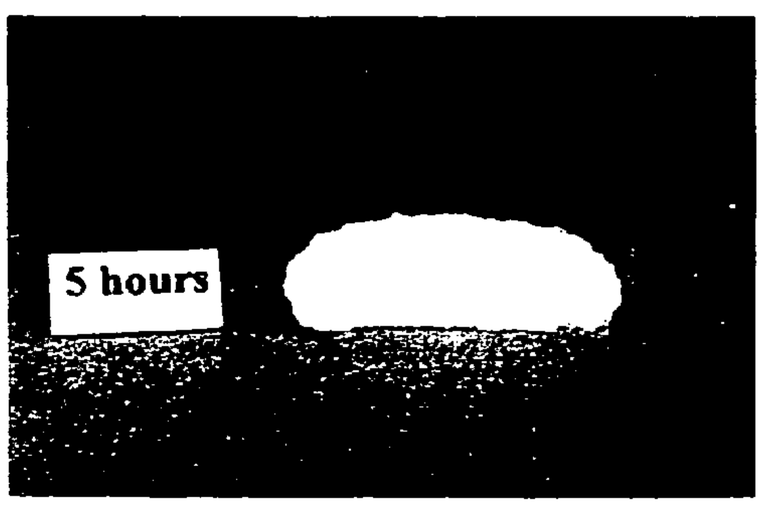

FRAME 6

FIG. 1

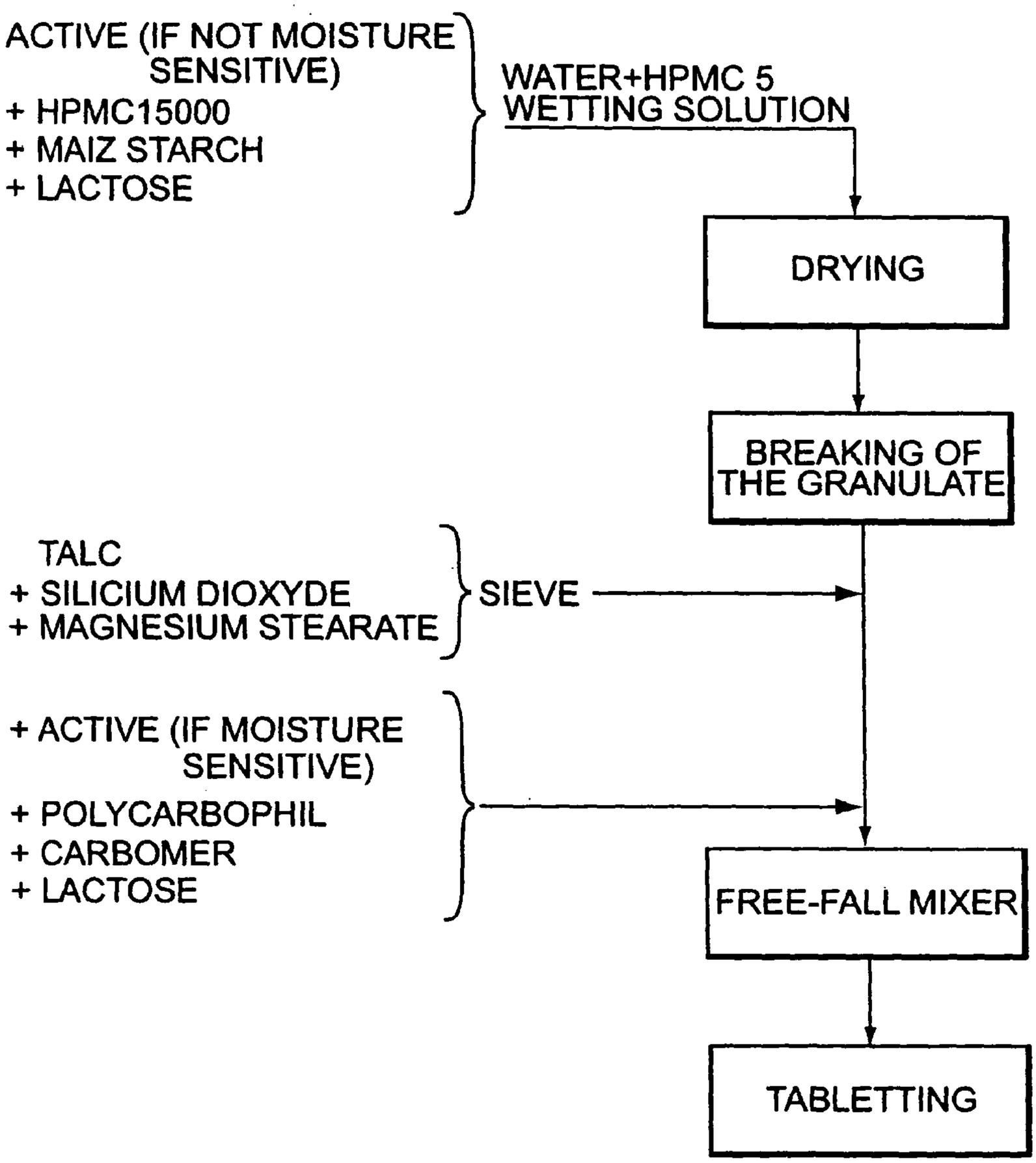
ACTIVE (IF NOT MOISTURE SENSITIVE)
+ HPMC15000
+ MAIZ STARCH
+ LACTOSE
WATER+HPMC 5
WETTING SOLUTION
DRYING
BREAKING OF THE GRANULATE
TALC
+ SILICIUM DIOXYDE
+ MAGNESIUM STEARATE
SIEVE
+ ACTIVE (IF MOISTURE SENSITIVE)
+ POLYCARBOPHIL
+ CARBOMER
+ LACTOSE
FREE-FALL MIXER
TABLETTING

FIG. 2

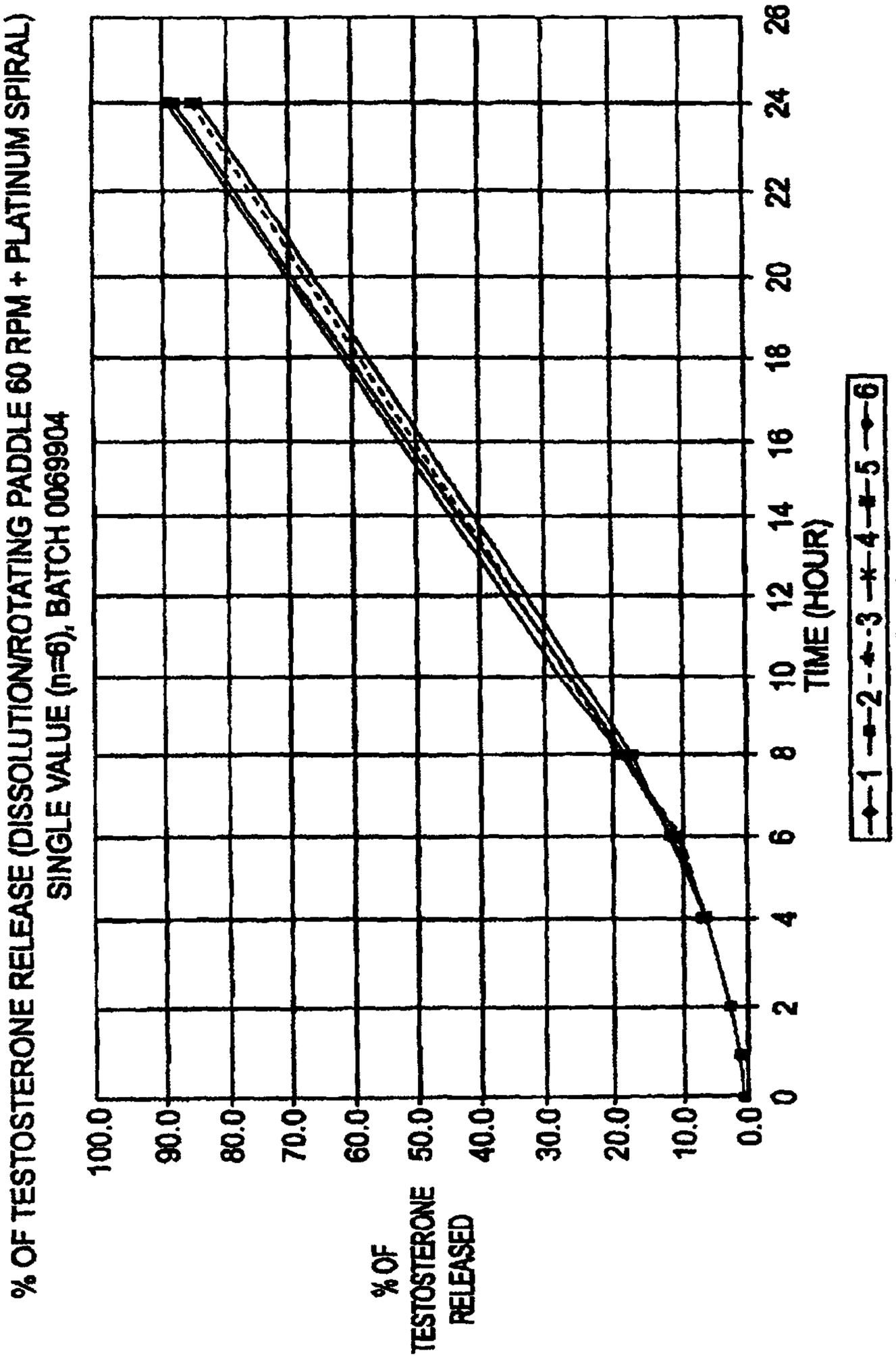
CHART 1
FORMULA 1
% OF TESTOSTERONE RELEASE (DISSOLUTION/ROTATING PADDLE 60 RPM + PLATINUM SPIRAL)
SINGLE VALUE (n=6), BATCH 0069904
% OF TESTOSTERONE RELEASED
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
TIME (HOUR)
1
2
3
4
5
6

FIG. 3

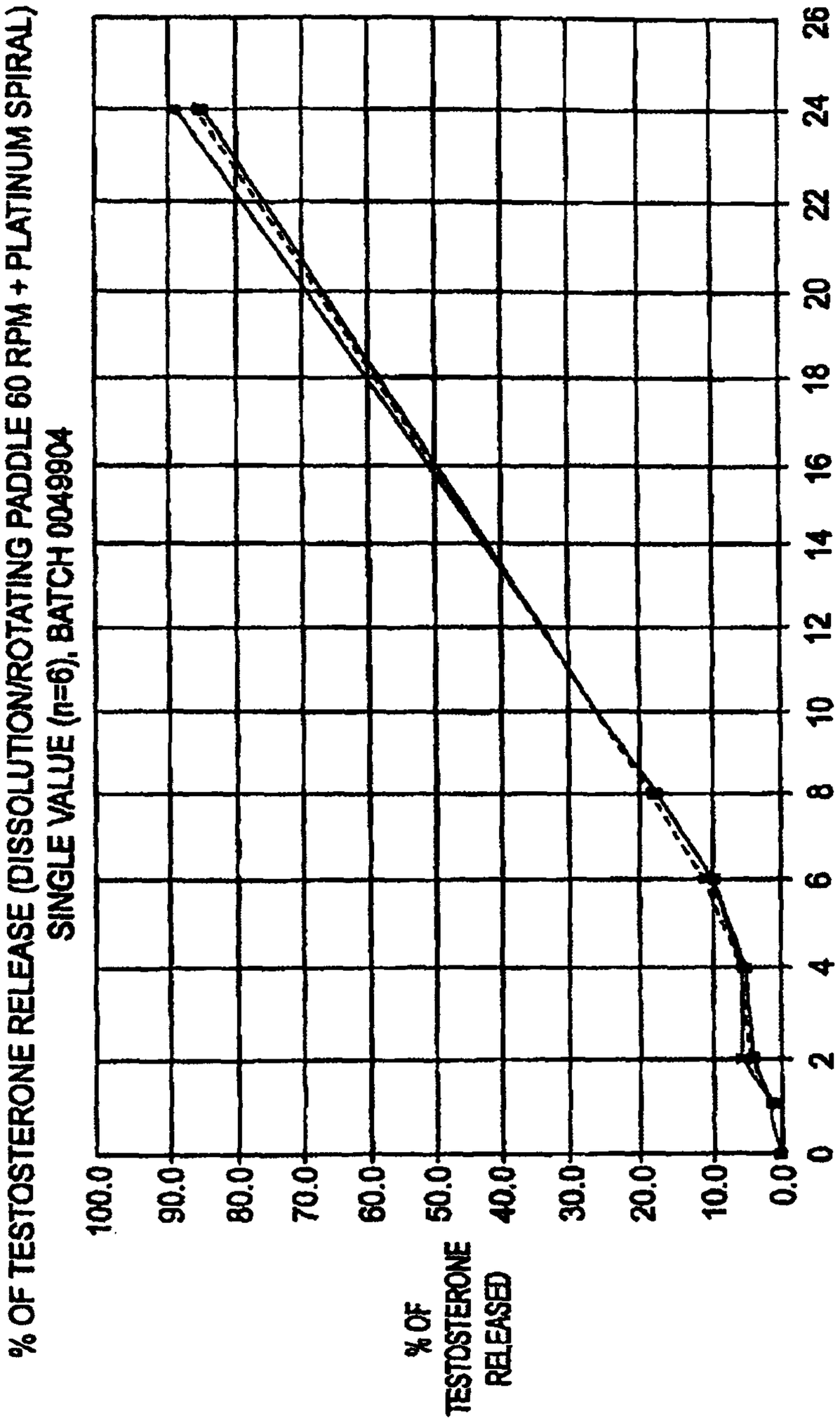
CHART 2
% OF TESTOSTERONE RELEASE (DISSOLUTION/ROTATING PADDLE 60 RPM + PLATINUM SPIRAL)
SINGLE VALUE (n=6), BATCH 0049904
% OF TESTOSTERONE RELEASED
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
TIME (HOUR)
1
2
3
4
5
6

FIG. 4

CHART 3

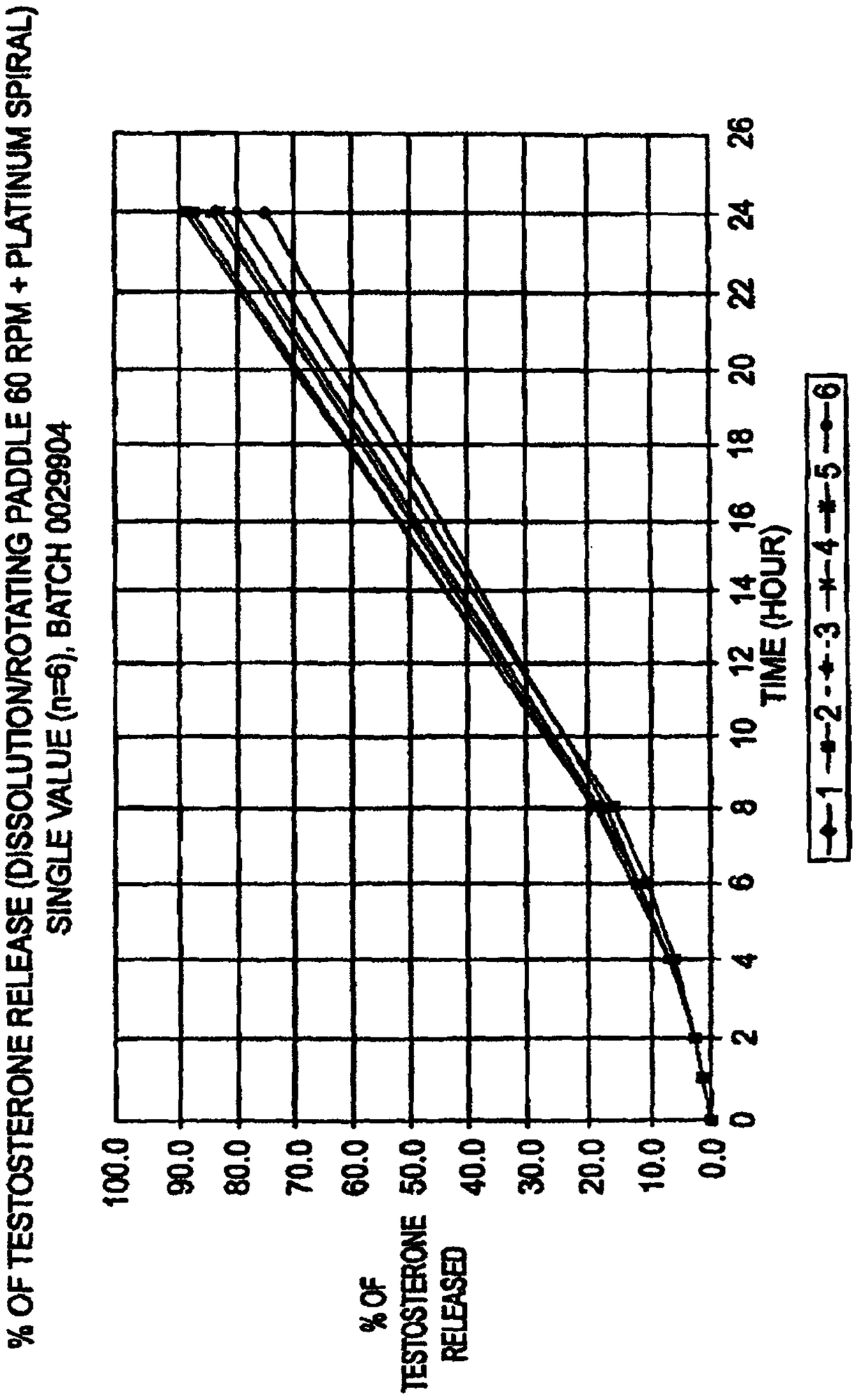
% OF TESTOSTERONE RELEASE (DISSOLUTION/ROTATING PADDLE 60 RPM + PLATINUM SPIRAL)
SINGLE VALUE (n=6), BATCH 0029904
% OF TESTOSTERONE RELEASED
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
TIME (HOUR)
1
2
3
4
5
6

FIG. 5

CHART 4

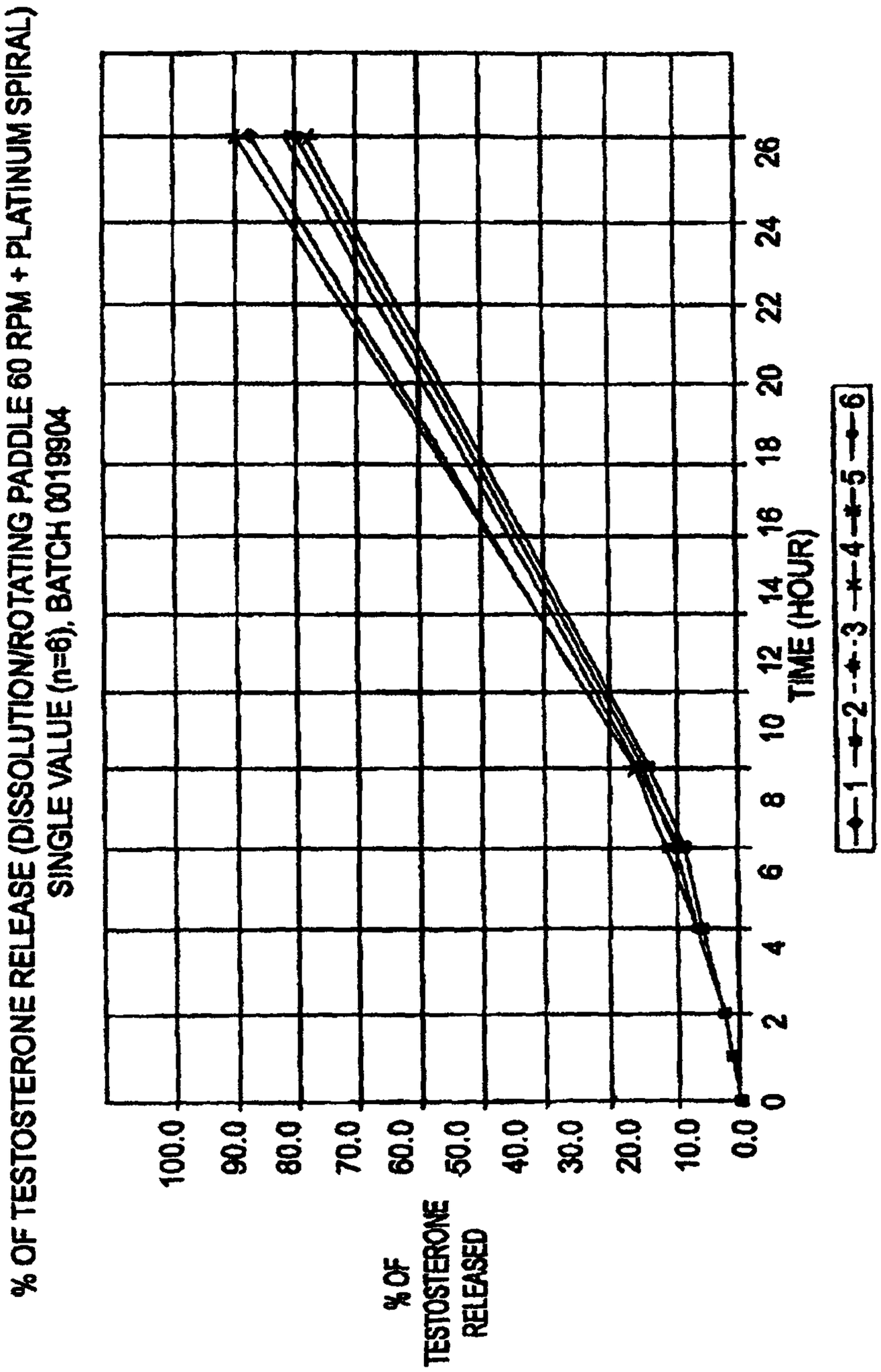
% OF TESTOSTERONE RELEASE (DISSOLUTION/ROTATING PADDLE 60 RPM + PLATINUM SPIRAL)
SINGLE VALUE (n=6), BATCH 0019904
% OF TESTOSTERONE RELEASED
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
TIME (HOUR)
1
2
3
4
5
6

FIG. 6

BIOADHESIVE PROGRESSIVE HYDRATION TABLETS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 10/421,840, filed Apr. 24, 2003, which claims the benefit of U.S. Provisional Application No. 60/376,545, filed May 1, 2002 and is a continuation-in-part of U.S. application Ser. No. 09/877,218, filed Jun. 11, 2001, now U.S. Pat. No. 6,624,200, which is a continuation-in-part of U.S. application Ser. No. 09/596,073, filed Jun. 16, 2000, now abandoned, which is a continuation-in-part of U.S. application Ser. No. 09/379,310, filed Aug. 23, 1999, now U.S. Pat. No. 6,248,358, which claims the benefit of provisional application Ser. No. 60/097,843, filed Aug. 25, 1998. The content of each of these patents and applications is expressly incorporated herein by reference thereto.

FIELD OF THE INVENTION

The present invention relates to bioadhesive, bioerodible compositions for the extended and controlled release of active ingredients (i.e., treating agents). More particularly, the present invention relates to progressive hydration tablets for adhesion to the wall of a body cavity for the sustained release of active ingredients without premature degradation or metabolism of the active ingredients caused by moisture, enzymes or pH effects.

BACKGROUND OF THE INVENTION

Medications and other pharmaceutical products have traditionally been administered in doses via oral ingestion, nasal sprays or injections. These delivery methods are not always effective for patients needing a prolonged and constant supply of an active ingredient delivered to the bloodstream, for example if the treating agent is particularly sensitive to moisture, pH, or enzymes. As used herein, with regard to treating agents, the term "sensitive" to moisture, pH, or enzymes means a treating agent that is metabolized or otherwise degraded when exposed to moisture, pH or enzymes such as upon administration to a body cavity. Depending on the degree of sensitivity for a particular treating agent, the length of time and the degree of exposure (for example, the amount of water present) will determine whether a significant amount of the treating agent is metabolized or degraded. The particular degree of sensitivity for each treating agent should also be kept in mind during manufacture. During manufacture, sensitivity to enzymes is normally not an issue, but moisture or even pH during manufacture can be a problem for certain treating agents. A treating agents' sensitivity to moisture or pH determines the time and degree of contact that a particular treating agent may have with moisture or an adverse pH during the manufacturing process, without undergoing substantial degradation. Therefore, the method of manufacture should take into account the particular treating agents' degree of sensitivity.

Particularly difficult delivery schedules are those that require dosing during sleep time hours. For these patients, intravenous ("IV") lines, slow-dissolving pills, and suppositories or transdermal patches have been prescribed. However, the inconvenience and discomfort of IVs, the short life span of many ingested active ingredients from gastrointestinal degradation or first-pass liver metabolism, and the inability of many products to be comfortably delivered transdermally in

suitable doses or in controlled concentrations have proven these methods frequently unsatisfactory.

Previous artisans have attempted to meet the needs of the art by developing products for the transmucosal administration of active ingredients. For example, certain active ingredients can be administered quickly into the bloodstream via the walls of a body cavity, such as the buccal or vaginal cavities, without the risk of first pass hepatic degradation. Generally, delivery of active ingredients through mucosal surfaces may be enhanced by the use of bioadhesive formulations. However, one particular area where those in the art have attempted, but heretofore failed, to meet the needs of the art is in developing a bioadhesive tablet useful for sustained release applications without risking degradation of the active ingredient before it is absorbed.

"Sustained release" generally refers to continuous or sporadic release of an active ingredient over an extended time after a single administration, whereby the level of active ingredient available to the host patient over a period of time. "Controlled release" is a different issue. A drug could be released over 72 hours, but hour-to-hour variation in the rate of release could be random, for example 600% or more. Such a formulation would be characterized as sustained but not controlled release (unless the pattern of release was intentional rather than random). "Controlled release" is not sporadic, but a constant or ordered release of the drug over time. For example, the release can often be maintained at some constant level over time or alternatively the release of the active ingredient could be controlled over a period of time wherein the level of active ingredient available to the host (bioavailability) may intentionally be at a variable but predetermined level at a particular instant in time of treatment, for example in an effort to mimic natural fluctuations in level.

The sustained release bioadhesive tablets known in the art can be generally broken down into two categories: (1) tablets consisting of water soluble carbomers, and (2) tablets consisting of insoluble polymers. Both types of tablets have proven unsatisfactory for many applications. For example, numerous artisans have attempted to formulate a suitable sustained release bioadhesive tablet from water soluble carbomers, such as carbomer 934P or CARBOPOL™ 974 resin (commercially available from B.F. Goodrich, Cleveland, Ohio). However, such tablets often are only able to adhere to the wall of a body cavity for short periods of time, e.g., six hours or less. Also, these tablets are easily dislodged from the wall of a body cavity and thus place patients using such tablets buccally at risk of asphyxiation. Furthermore, these prior art tablets inherently become hydrated relatively quickly and thus may prematurely expose the reservoir of active ingredient to degradation by moisture or by enzymes from the host environment such as from bacteria in the septic oral or vaginal cavities.

Similarly, tablets comprised of insoluble polymers, such as polycarbophil, have proven unsuitable for many applications. For example, although polycarbophil-containing tablets are capable of prolonged attachment to the wall of a body cavity, such tablets do not adhere immediately, making them impractical for certain treatments such a buccal delivery of active ingredients to patients during sleep time hours. Further, such tablets often do not soften sufficiently to provide comfort and imperceptibility, or provide safety from potential aspiration of the tablet.

Furthermore, for example, neither type of prior art tablet is particularly suitable for treating many conditions. As alluded to previously, there are numerous medical conditions in which a sustained and/or controlled release of active ingredients) is desired for any of numerous reasons including, for

example, to alleviate the impact of first-pass hepatic metabolism of the active ingredient or the risk of premature degradation of the active ingredient by moisture, pH effects, or enzymes, or to attain the comfort and convenience offered by a suitable bioadhesive tablet. Such conditions include, but are not limited to, for example, those needing treatment with an active ingredient that may be, but is not limited to, a glycoprotein, protein, sex hormone, anti-hormone, nitrate, beta-agonist, beta-antagonist, opioid, opioid-antagonist, antidepressant, HMG CoA (3-hydroxy-3-methylglutaryl Coenzyme A) reductase inhibitor, antihistamine, ACE (angiotensin converting enzyme) inhibitor, and/or prostaglandin. Heretofore the art has required such patients to undergo the more invasive and less suitable techniques and methods of delivery described above.

To illustrate the need in the art, consider hypogonadal men, for example. Hypogonadism in man is characterized by a deficiency or absence of endogenous testosterone production. Abnormally low levels of testosterone may place men at risk of "Andropause", wherein men are at greater risk of cardiovascular disease, Alzheimer's disease, and osteoporosis.

Testosterone has traditionally been used to treat hypogonadal men. However, to be most effective, the treatment must be capable of complete physiologic testosterone replacement. Moreover, the treatment must be capable of providing sustained levels of testosterone through the night. Preferably, the treatment provides physiologic levels with circadian delivery of testosterone, with lower levels released during the night and peak levels occurring during the early morning. Transdermal testosterone patches typically produce only subphysiologic levels and thus incomplete relief. Similarly, the prior art buccal tablets heretofore described would be ineffective or impractical for such sustained testosterone delivery.

The hormone testosterone, like many other drugs, including many other proteins and glycoproteins, undergoes high first pass hepatic metabolism. Accordingly, as will be appreciated by one of ordinary skill in the art, buccal or vaginal tablets consisting of materials that are incapable of keeping the interior reservoir of the tablet in the dry state for prolonged periods are inherently incapable of preventing dissolution and swallowing, or of preventing dissolution and rapid absorption of the active ingredient through the mucosa. Furthermore, as will be appreciated by one of ordinary skill in the art, tablets which are unable to quickly adhere to the target area or are able to become dislodged are especially impractical for treatments which use night-time delivery, such as testosterone treatment.

Active ingredients such as testosterone may also undergo undesired metabolism. For example, 5α-reductase converts testosterone to 5α-dihydrotesterone (DHT). DHT may cause adverse effects such as hair loss and prostate disorders. Similarly, 5α-reductase may metabolize other active ingredients such as progesterone.

Various testosterone formulations have been developed to circumvent the problems inherent in rapid clearance of orally and parenterally administered agents. These include transdermal preparations, pellets for subcutaneous implantation, biodegradable microcapsule formulations for injection, and inclusion complexes that enhance sublingual absorption of the hormone. Of these, the transdermal skin patches and gel products are probably the most widely used. Under optimal conditions, they are intended to approximate the physiological pattern of hormone levels throughout the day and provide an alternative to parenteral therapy. However, the scrotal preparation causes a disproportionate increase in plasma dihydrotestosterone (DHT) to a level that is 30 to 40% that of testosterone, presumably because of the high level of 5α-reductase in scrotal skin. Other skin patches likewise produce high levels of DHT. Such increases in serum DHT have also been reported after treatment with the extremely long-acting parenteral testosterone ester testosterone buciclate and with the oral ester testosterone undecanoate. Williams Textbook of Endocrinology, 9th Ed., W.B. Saunders Company, p. 853. Thus, the present invention advantageously avoids the side effects that may be caused by 5α-reductase's metabolism of active ingredients.

Furthermore, as will be appreciated by one of ordinary skill in the art, the advantages of a sustained release, bioadhesive tablet according to the present invention are useful for much more than the treatment of hypogonadism in men. For example, patients often require sustained release hormone treatment for various conditions. In addition, other medications, such as steroids for treating such conditions as asthma, involve treatments where desired peak levels are at night during sleep-time hours. Accordingly, one of ordinary skill in the art will appreciate that there exists a long-felt, yet unresolved, need to develop a bioadhesive, sustained release tablet to satisfy the aforementioned needs of the art, including, but not limited to, the delivery of therapeutically effective amounts of an active ingredient which may be metabolized or otherwise degraded by moisture, enzymes, or pH effects, such as, for example, glycoproteins, proteins, sex hormones, anti-hormones, nitrates, beta-agonists, beta-antagonists, opioids, opioid-antagonists antidepressants, HMG CoA reductase inhibitors, antihistamines, ACE inhibitors, and/or prostaglandins.

For example, an advantage to administering treating agents such as terbutaline (especially for sleep time administration) through a sustained release bioadhesive tablet according to the instant invention is that such administration provides controlled, extended release to help prevent high peak blood serum levels of the terbutaline. This is particularly useful when the treating agent, such as terbutaline, is associated with adverse side effects at high blood serum levels.

U.S. Pat. No. 5,543,150 discloses a method of progesterone delivery. The formulation includes a cross-linked polycarboxylic acid polymer to deliver progesterone locally to the vagina. There is no disclosure, however, of a formulation that includes the polymer in an amount and in combination with other polymers to facilitate progressive hydration of the polymers to provide extended release of the progesterone.

U.S. Pat. No. 6,063,404 discloses a bioadhesive tablet containing at least one bioadhesive adjuvant and at least one lubricant, with at least one surface of the tablet having concentric or parallel, straight, and/or curved depressions. These depressions increase the surface area of the tablet for contact with the mucosa thereby permitting immediate release, rather than extended release, of the active ingredient. This tablet does not include both a water soluble polymer and a water insoluble, water-swellable cross-linked polycarboxylic polymer, so that the tablet does not progressively hydrate.

Thus, there is a need for extended release progressive hydration formulation for delivering active agents to a patient in need of such treatment, and such formulations are now provided by the present invention.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a bioadhesive controlled, sustained release progressive hydration pharmaceutical composition for delivering an active ingredient to a mucosal surface of a mammal. The composition preferably includes an effective amount of an active ingredient, a water

insoluble, water-swellable cross-linked polycarboxylic polymer, and a water soluble polymer.

The pharmaceutical composition is typically formulated as a tablet for delivery of the active ingredient via the buccal, vaginal, nasal, or rectal cavity, although other formulations and delivery modes will be appreciated by one of ordinary skill in the art and are within the scope of the invention. In one preferable embodiment of the invention the composition is formulated for delivery via the buccal cavity and gelifies or swells to avoid asphyxiation during use.

Generally, the active ingredient includes one or more glycoproteins, proteins, sex hormones, anti-hormones, nitrates, beta-agonists, beta-antagonists, opioids, opioids-antagonists, antidepressants, HMG CoA reductase inhibitors, antihistamines, ACE inhibitors, prostaglandins, or other agent desired to be administered in this manner. In a preferred embodiment of the invention the active ingredient includes at least one treating agent selected from the following group: testosterone, progesterone, terbutaline, prostaglandin E_2, or desmopressin.

In a preferred embodiment, the pharmaceutical composition includes testosterone in an amount of about 0.5 mg to 45 mg per unit dosage of the composition and more preferably in an amount of about 3 mg and 30 mg per unit dosage.

In another preferred embodiment of the invention, the pharmaceutical composition includes terbutaline in an amount of about 1 mg to 4 mg per unit dosage of the composition.

In a further embodiment of the invention, the pharmaceutical composition includes desmopressin in an amount of about 0.025 mg to 0.2 mg per unit dosage of the composition, and typically is formulated to be delivered via the buccal cavity.

In yet another embodiment of the invention, the active ingredient is prostaglandin E_2 in an amount of up to about 2 mg per unit dosage of the compositions. In a preferred embodiment, the dosage is about 0.5 mg per unit dosage of the composition.

In a particularly preferred embodiment of the invention, the pharmaceutical composition is formulated to deliver the testosterone through the mucosal surface to provide a blood serum concentration ratio of testosterone to 5α-dihydrotestosterone (DHT) of about 9 to 1 to about 12 to 1 in the bloodstream of the mammal being treated.

Additionally, the present invention also provides a method of delivering an active ingredient to a mucosal surface of a mammal. The method includes the step of administering the active ingredient via a progressive hydration bioadhesive composition. The progressive hydration bioadhesive composition is preferably administered via the buccal, vaginal, nasal, or rectal cavity and preferably includes a water insoluble, water-swellable cross-linked polycarboxylic polymer; a water soluble polymer, and an active ingredient.

The invention also relates to a bioadhesive controlled, sustained release progressive hydration pharmaceutical composition for delivering an active ingredient to a mucosal surface of a mammal, that includes an effective amount of an active ingredient, a water insoluble, water-swellable cross-linked polycarboxylic polymer, and a water soluble polymer, wherein the composition is formulated with amounts of the polymers effective to allow the composition to progressively hydrate when contacting a mucosal surface of a mammal to provide an extended release of the active ingredient to the mammal over time. In a preferred embodiment, the composition provides extended release of the active ingredient beyond its immediate release dosage form.

In another embodiment, the invention relates to a method for delivering an active ingredient to the bloodstream of a mammal through a mucosal surface by progressive hydration which includes administering to a mucosal surface of a mammal in need of receiving the active ingredient a composition that includes effective amounts of the active ingredient, a water insoluble, water-swellable cross-linked polycarboxylic polymer, and a water soluble polymer, such that the composition is formulated to progressively hydrate when contacting the mucosal surface of a mammal, with the progressive hydration of the composition providing an extended release of the active ingredient to the mammal over time. The invention is typically not limited to any particular active ingredient or amount of any active or inactive ingredient, so long as the amount is effective for the purpose for which it is administered.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a series of photographs depicting the progressive hydration of a bioadhesive tablet according to the invention.

FIG. **2** is a flowchart depicting a presently preferred method of making bioadhesive tablets according to the invention.

FIGS. **3** through **6** depict the testosterone release rate for four different progressive hydration formulations, as discussed further below.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a bioadhesive tablet that adheres immediately or almost immediately to the target tissue area of a body cavity and generally stays attached substantially throughout treatment. In accordance with this aspect of the invention, there is provided a bioadhesive tablet that can stay attached and deliver active ingredients in the buccal cavity for as much as eighteen hours or more. In accordance with a related aspect of the invention, there is provided a bioadhesive tablet that can stay attached and deliver active ingredients vaginally for as much as 72 hours or more. Depending on the active ingredient and the desired convenience, the bioadhesive tablet will preferably stay attached and deliver active ingredients for at least 12 hours, more preferably for at least 24 hours, and most preferably for at least 48 hours. In another preferable embodiment, the bioadhesive tablet would stay attached and deliver active ingredients for at least about 3.5 days.

The invention provides a bioadhesive tablet that progressively hydrates, whereby the inner core of the tablet remains protected from moisture and the surrounding environment. In accordance with this aspect of the invention there is provided a bioadhesive tablet suitable for sustained release use in mucosal and other body cavities even with active ingredients comprising proteins or glycoproteins or other treating agents that are particularly susceptible to metabolism, or to enzymatic, pH, or moisture-induced degradation.

The invention further provides a bioadhesive tablet having both controlled and sustained release properties due to a tablet formulation wherein the active ingredient is only progressively made bioavailable over an extended time period by the progressive hydration of the tablet's dry reservoir of active ingredient. In a preferred embodiment, the composition would deliver the active ingredient in an extended release dosage form for a period of time beyond its typical dosage. As used herein, the term "extended release" refers to a dosage form that allows for the reduction in dosing frequency as compared to that presented by a conventional dosage form,

e.g., a solution or immediate release dosage form. For example, for desmopressin, the composition would deliver the drug beyond its immediate release dosage form.

The invention also provides a bioadhesive tablet according to the invention that also gelifies and/or swells to help protect a patient using the tablet buccally from asphyxiation, particularly a sleeping patient undergoing treatment.

Methods of making bioadhesive tablets represent another embodiment of the invention. In accordance with one aspect, there is provided a method of making bioadhesive tablets wherein an active ingredient resistant to premature metabolism and/or degradation is added in the first and/or second step (manufacture of granulate). In accordance with a related aspect, there is provided a method of making bioadhesive tablets wherein an active ingredient prone to premature metabolism and/or degradation is added in the second step (manufacture of the tableting mixture) after the granulate is dried and sieved. Of course, other concerns or factors may affect the choice of which step or steps are appropriate for adding a particular active ingredient.

It is yet another feature of the invention to provide methods of using bioadhesive tablets as described herein, to administer a sustained release formulation of a hormone, such as testosterone, to a patient.

The inventors of the present invention have discovered, quite unexpectedly, that these embodiments and other features for the invention may be achieved by making and using tablets comprising an active ingredient, one or more bioadhesive water soluble polymers (e.g., carbomer 974P or 934P, or CARBOPOL™ 974P), and one or more bioadhesive, water insoluble water swellable cross-linked polycarboxylic polymers, preferably polycarbophil (e.g., NOVEON®, available from B.F. Goodrich Specialty Polymers of Cleveland, Ohio), and preferably hydroxypropylmethyl cellulose (HPMC), lactose, corn starch and other standard tablets ingredients, such as magnesium stearate, talc, and silica.

Other potential ingredients in the formulation include polyethers, such as polysorbate 80, sodium lauryl sulfate, polyethylene glycols, such as cetomacrogol, sodium citrate.

The specific drug delivery formulation chosen and used in the examples below comprises a cross-linked polycarboxylic acid polymer formulation, generally described in U.S. Pat. No. 4,615,697 to Robinson (hereinafter "the '697 patent"), which is incorporated herein by reference. In general, at least about eighty percent of the monomers of the polymer in such a formulation should contain at least one carboxyl functionality. The cross-linking agent should be present at such an amount as to provide enough bioadhesion to allow the system to remain attached to the target epithelial surfaces for a sufficient time to allow the desired dosing to take place.

For vaginal administration, such as in the examples below, preferably the formulation remains attached to the epithelial surfaces for a period of at least about twenty-four to forty-eight hours. Such results may be measured clinically over various periods of time, by testing samples from the vagina for pH reduction due to the continued presence of the polymer. This preferred level of bioadhesion is usually attained when the cross-linking agent is present at about 0.1 to 6.0 weight percent of the polymer, with about 1.0 to 2.0 weight percent being most preferred, as long as the appropriate level of bioadhesion results. Bioadhesion can also be measured by commercially available surface tensiometers utilized to measure adhesive strength.

The polymer formulation can be adjusted to control the release rate of the β-adrenergic agonist, such as terbutaline, by varying the amount of cross-linking agent in the polymer. Suitable cross-linking agents include divinyl glycol, divinylbenzene, N,N-diallylacrylamide, 3,4-dihydroxy-1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene and similar agents.

A preferred polymer for use in such a formulation is Polycarbophil, U.S.P., which is commercially available from B.F. Goodrich Speciality Polymers of Cleveland, Ohio under the trade name NOVEON®. The United States Pharmacopeia, 1995 edition, United States Pharmacopeial Convention, Inc., Rockville, Md., at pages 1240-41, indicates that polycarbophil is a polyacrylic acid, cross-linked with divinyl glycol.

Other useful bioadhesive polymers that may be used in such a drug delivery system formulation are mentioned in the '697 patent. For example, these include polyacrylic acid polymers cross-linked with, for example, 3,4-dihydroxy-1,5-hexadiene, and polymethacrylic acid polymers cross-linked with, for example, divinyl benzene.

Typically, these polymers would not be used in their salt form, because this would decrease their bioadhesive capability. Such bioadhesive polymers may be prepared by conventional free radical polymerization techniques utilizing initiators such as benzoyl peroxide, azobisisobutyronitrile, and the like. Exemplary preparations of useful bioadhesives are provided in the '697 patent.

Bioadhesive, progressive hydration tablets according to the invention may be used with any suitable active ingredient and may be used to deliver a therapeutic amount of the active ingredient to a patient at controlled rates for sustained periods of time. Tablets according to the invention may also be constructed in any suitable shape and any suitable size consistent with the intended therapeutic use of the tablet.

Tablets according to the invention may comprise any suitable amount of active ingredient. Suitable amounts of active ingredient according to the invention may be from minuscule amounts to about 50%, or more. As will be appreciated by one of ordinary skill in the art, "minuscule amounts" is intended to cover those amounts of potent active ingredients that are disproportionately small relative to the tablet, for example, when only a few micrograms of active ingredient are to be delivered via a tablet weighing over a hundred milligrams. Accordingly, one of ordinary skill in the art will appreciate that any amount of active ingredient, in any ratio, is within the scope of the present invention.

The tablet thus comprises a sustained release active ingredient delivery system comprising the water insoluble, water-swellable cross-linked polycarboxylic polymer, and the water soluble polymer, wherein the delivery system includes amounts of the polymers which, in combination, are effective to allow the composition to progressively hydrate when contacting a mucosal surface of a mammal to provide an extended release of the active ingredient to the mammal over a time period of time beyond the immediate release form of the drug. The optimum amounts and specific types of such polymers to use in the formulation can be selected by the skilled artisan for the particular formulation or can be determined by routine testing.

The balance of the tablet according to the invention may comprise water soluble polymer(s) and water insoluble cross-linked polycarboxylic polymer(s). Also, according to the invention, exemplary tablets preferably have between about 1% and about 75% by weight water soluble polymer (preferably carbomer 974P) and between about 0.5% and about 10% by weight water insoluble, water-swellable cross-linked polycarboxylic polymer (preferably polycarbophil, at about 0.5 to 3% by weight). In accordance with the invention, such exemplary tablets also preferably include between about 5% and about 50% cellulose. Also in accordance with the invention, presently preferred tablets may have between about

0.5% and about 25% by weight starch. These preferred tablets may also have between about 1% and about 50%, or as much as 95%, by weight lactose.

Furthermore, according to the invention, preferred tablets may comprise from about 0.01% up to about 2% silica; and/or up to about 5% to 8% by weight talc; and/or up to about 2.5% by weight magnesium stearate.

Accordingly, one of ordinary skill in the art will also appreciate that the components of the tablets can be varied to suit a particular purpose. For example, the inventors of the present invention have discovered that one way of increasing (decreasing) the time it takes a progressive hydration tablet to hydrate is by increasing (decreasing) the amount of lactose and/or starch and decreasing (increasing) the amount of water soluble polymer. Alternatively, the density of the tablet may be altered to affect the hydration period.

Active ingredients suitable for use in the present invention include any active ingredient or ingredients requiring sustained or controlled release, any active ingredient or ingredients requiring extended protection from premature degradation by moisture, pH effects, or enzymes, or any active ingredient requiring administration to a patient with protection from first-pass hepatic metabolism. Exemplary active ingredients suitable for use with the present invention include, but are by no means limited to: (1) glycoproteins, such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (HCG), thyroid-stimulating hormone (TSH), and the like; (2) proteins, such as GnRH (agonist and antagonist), desmopressin, oxytocin analogs, insulin analogs, TRH analogs, somatostatin analogs, tissue plaminogen activator (TPA), growth hormone releasing hormone (GHRH), corticotropin-releasing hormone analogs (CRH analogs), and the like; (3) sex hormones, such as estradiol, testosterone, progesterone, other estrogenic and progestogenic compounds, and the like; (4) anti-hormones and selective estrogen and progestin receptor modulators, such as tamoxifen, mifepristone, raloxifene, and the like; (5) nitrates, such as nitroglycerin, isosorbide, erythrityl tetranitrate, pentaerythritol tetranitrate, and the like; (6) beta-agonists, such as terbutaline, albuterol, pirbuterol, bitolterol, ritodrine, and the like; (7) beta-antagonists, such as propranolol, metoprolol, nadolol, atenolol, timolol, esmolol, pindolol, acebutolol, labetalol, and the like; (8) opioids, such as morphine, hydromorphone, oxymorphone, codeine, hydrocodone, oxycodone, levorphanol, levallorphan, buprenorphine, fentanyl, nalbuphine, butorphanol, pentazocine, and the like; (9) opioids-antagonists, such as naloxone, nalmefene, and the like; (10) antidepressants, such as amitriptyline, amoxapine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protripyline, trimipramine, fluoxetine, trazodone, and the like; (11) HMG CoA reductase inhibitors, such as lovastatin, mevastatin, simvastatin, pravastatin, atorvastatin, and the like; (12) antihistamines, such as loratadine, chlorpheniramine maleate, brompheniramine maleate, diphenhydramine, dimenhydrinate, carbinoxamine, promethazine, tripelannamine, and the like; (13) ACE inhibitors, such as captopril, enalapril, lisinopril, and the like; (14) prostaglandins, are a class of naturally occurring chemically related, long-chain hydroxy fatty acids, such as prostaglandin E_2 ("PGE_2"), PGE_1, PGA_1, PGB_1, $PGF_{1\alpha}$, 19-hydroxy-PGA_1, 19-hydroxy-PGB_1, PGA_2, PGB2, 19-hydroxy-PGA_2, 19-hydroxy-PGB_2, PGE_3, $PGF_{3\alpha}$; semisynthetic or synthetic derivatives of natural prostaglandins, including mioprostol, carboprost tromethamine, dinoprost tromethamine, dinoprostone, lipoprost, gemeprost, metenoprost, sulprostone and tiaprost; analogues thereof and the like; (15) non-steroidal anti-inflammatory drugs (NSAIDS), such as diclofenac, etodolac, fenoprofen, lurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxin, oxaprozin, piroxicam, sulindac, tolmetin, and the like; (16) anti-infectives; (17) anesthetics, such as lidocaine, cocaine, chloroprocaine, tetracaine, prilocalne, mepivacaine, buipivacaine, levobupivacaine, articaine, ropivacaine, phenol, benzocaine, pramoxine, dyclonine, etidocaine, procaine, proparacaine, dibucaine, and pramoxine; (18) immune system modifiers such as imiquimod and the like; (19) muscarinic agonists and antagonists such as bethanecol and oxybutynin and the like; (20) anti-neoplastic agents including alkylating agents such as melphalan, anti-metabolites such as fluorouracil, and natural products such as vinca alkaloids and bleomycin as well as agents such as cisplatin and the like; (21) vitamin K; (22) ondansetron; (23) levocarnitine; (24) anti-fungals; (25) carbamide peroxide; (26) dopamine antagonists (bromocriptine); (27) bisphosphonates: (28) nicotine; (29) anti-virals (acyclovir); (30) anti-diabetagenics (metformin); (31) peptides (octreotide, desmopressin, GNRH, other proteins); (32) insulin; (33) anti-Parkinson agents (levodopa); (34) low molecular weight heparins; and (35) antimicrobials such as metronidazole and the like. Accordingly, one of ordinary skill in the art will appreciate that tablets according to the invention may be used with a wide variety of active ingredients to treat a wide variety of conditions.

The present invention also provides a pharmaceutical composition comprising an effective amount of active ingredient, a water insoluble, water-swellable cross-linked polycarboxylic polymer, and a water soluble polymer, wherein said composition is formulated to deliver said active ingredient to the bloodstream of a mammal through a mucosal surface of the mammal.

The present invention further provides a method of delivering to a mammal an active ingredient that is metabolized by 5α-reductase, comprising administering said active ingredient via a progressive hydration bioadhesive composition through a mucosal surface of the mammal.

In addition, the present invention provides a composition for delivering to the bloodstream of a mammal an active ingredient that is metabolized by 5α-reductase, comprising a water insoluble cross-linked polycarboxylic polymer, and a water soluble polymer, wherein said composition is formulated to deliver said active ingredient through a mucosal surface of the mammal.

In addition, the present invention provides a bioadhesive progressive hydration pharmaceutical composition comprising: an effective amount of a treating agent, a water insoluble, water-swellable cross-linked polycarboxylic polymer, and a water soluble polymer, wherein said composition is formulated to deliver said treating agent to the bloodstream of a mammal through a mucosal surface of the mammal.

In addition, the present invention provides a bioadhesive progressive hydration pharmaceutical composition comprising: an effective amount of terbutaline, progesterone, testosterone, PGE_2, or desmopressin; a water insoluble, water-swellable cross-linked polycarboxylic polymer; and a water soluble polymer; wherein said composition is formulated to deliver said terbutaline, progesterone, testosterone, PGE_2, or desmopressin, to the bloodstream of a mammal through a mucosal surface of the mammal.

Furthermore, the present invention provides a method of delivering to a mammal an effective amount of a treating agent, including without limitation, testosterone, terbutaline, progesterone, PGE_2, or desmopressin, via a progressive hydration bioadhesive pharmaceutical composition through a mucosal surface of the mammal, comprising said treating

agent, a water insoluble, water-swellable cross-linked polycarboxylic polymer, and a water soluble polymer.

Preferably, the compositions of the present invention are formulated to deliver said active ingredient via the mammal's vaginal, buccal, nasal, or rectal cavity.

The aforementioned and other aspects of the invention will become more clear by reference to the Figures and descriptions of preferred embodiments.

A preferred embodiment of the invention is depicted in FIG. **1**. As shown in the first-frame of FIG. **1**, before the tablet is administered all of the active is in the dry state and thus, not subject to the deleterious action of moisture, pH effects, enzymes or other chemicals. It is also not available for absorption (bioavailable). As shown in frames 2-6 of FIG. **1**, over time the residual portion of the active remains in the dry state which both protects it from water and the immediate environment as well as allowing it to serve as a reservoir for the sustained and controlled release of the active. Such a delivery system is well suited for the delivery of proteins, glycoproteins, and other drugs which must be protected from metabolism or during prolonged administration from enzymatic, pH, or moisture-induced degradation.

In a preferred embodiment, when used buccally, progressive hydration of the bioadhesive tablet protects the patient, should the tablet become dislodged, by gelifying and becoming heavier and thus less likely to float in the airway, risking aspiration. This makes this embodiment particularly well suited for agents that should reach their peak levels in the middle of the night, e.g., hormones like testosterone or steroids to treat asthma. According to the invention, the hydration of the tablet can preferably take hours (e.g. 12 to 24 hours) when formulated for buccal tablets or even days when formulated for vaginal use. As will be appreciated by one of ordinary skill in the art, prior art bioadhesive tablets do not protect the active ingredient from moisture, pH, or from enzymes produced by bacteria in the septic oral and vaginal orifices.

Furthermore, as will be appreciated by one of ordinary skill in the art following the teaching of the present application, the tablet can be sized, shaped and dosed to meet the needs of the particular treatment being undertaken. For example, the buccal bioadhesive tablet depicted in FIG. **1** was constructed to be only 9 mm in diameter for the comfort of the patient, but made capable of delivering 7 mg of testosterone per day, full physiologic level. By contrast, prior art transdermal patches were only capable of delivering 5 mg per day, in other words a sub-physiologic level.

A presently preferred method of manufacturing bioadhesive tablets is diagramed in FIG. **2**. The presently preferred method involves three steps as described below:

1. First Step: Manufacture of the Granulate.

Hydroxypropylmethyl cellulose 15000(=HPMC 15000) is mixed with corn starch and lactose and, in those cases where a particular active ingredient is not sensitive to moisture, the active ingredient is also added at this time. The mixture is wet with an aqueous solution of hydroxypropylmethyl cellulose 5 (=HPMC 5) and knead/granulated.

The granulate is dried in an oven under warm air (50° C.) until moisture content is less than 2.5%.

The dried granulate is broken with a stainless steel sieve oscillating granulator mesh size 1000 μm.

2. Second Step: The Tableting Mixture.

Talc, silicon dioxide magnesium stearate, and in a case of an active ingredient sensitive to moisture, the active ingredient is added. All is sieved through a sieving machine having aperture size 500 μm and then transferred into a free-fall mixer.

Addition of the granulate of step 1, followed by polycarbophil, carbomer and lactose. The whole is mixed until homogenous.

3. Third Step: Tableting.

The tableting mixture is compressed into tablets by means of a rotative tableting machine equipped with punches 9 mm flat on the upper side and curved (r=9 mm) on the lower side both with beveled edge. The tablets are dedusted and packed.

As depicted in FIG. **2**, an active ingredient that is not sensitive to moisture is preferably added during the manufacture of the granulate. However, alternatively, the active ingredient can be added during the second step after the granulate is dried and sieved. Also, as will be appreciated by one of ordinary skill in the art, this second method is particularly preferred when the active ingredient is sensitive to moisture.

In a presently preferred manufacturing process, the active ingredient is preferably protected from moisture. A wet granulation is made of lactose, corn starch and HPMC. Testosterone, polycarbophil, carbomer 974P, talc and magnesium stearate are added dry for the final compression.

Furthermore, as will be appreciated by one of ordinary skill in the art following the teaching of the present application, the materials of construction can be varied to optimize the desired characteristics of the tablet. For example, the present inventors have discovered that by progressively increasing the amount of lactose and corn starch and progressively decreasing the amount of carbomer 974P, the amount of time it takes a tablet to hydrate is progressively increased. Accordingly, as will be appreciated by one of ordinary skill in the art, tablets suited for specific treatments (i.e., specific active, specific dose, specific delivery time) can be manufactured.

These and other aspects of the invention may be more clearly shown by way of example.

Example 1

Testosterone Tablet

The following is an example of a formulation (Formulation 8, batch #00029906) designed for complete physiologic replacement of testosterone in men:

INGREDIENT	AMOUNT	% w/w
Testosterone	30.000 mg	24.0%
HPMC	26.250 mg	21.0%
Corn Starch	22.500 mg	18.0%
Monohydrated Lactose	30.125 mg	24.1%
Silica	1.250 mg	1.0%
Polycarbophil (Noveon)	3.125 mg	2.5%
Carbomer 974P	9.375 mg	7.5%
Talc	1.500 mg	1.2%
Magnesium stearate	0.875 mg	0.7%

Formulations like the one above produced sustained release in in-vitro dissolution tests. When used in female subjects formulas like this one also produce a sustained and controlled release of testosterone for 12 hours or more.

Testosterone formulations have resulted in mean blood serum concentration ratios of testosterone to 5α-dihydrotestosterone (DHT) of 9.25 and 9.29 to 1, to as high as about 12 to 1, in the bloodstream of said mammal. It is contemplated that this mean serum concentration ratio preferably is about 9 to 1 to about 12 to 1.

The individual ingredients are well known and readily available from suppliers known in the industry.

HPMC, or hydroxypropylmethylcellulose, is a swelling, dispersing agent. Alternates, which are well-known in the industry, include other water-swellable forms of cellulose and polymers. Microcrystalline cellulose is a form that is a well-known binder used in tableting.

Corn (maize) starch is a filler and binder. Alternates are well-known in the industry.

Lactose is a filler. Alternatives are well-known in the industry, and include, for example, mannitol and calcium phospate.

Silica, or silicon dioxide (silicium dioxide), acts as a suspending and thickening agent. Alternatives are well-known in the industry, and include, for example, caregeenan or sodium alginate.

Talc and magnesium stearate are lubricant powders commonly used in the manufacture of compressed tablets. Alternatives are well-known in the industry.

Carbomer 934P or 974P (or CARBOPOL™ 974P) is the water soluble polymer. This polymer provides the initial bioadhesion. Alternatives are well-known in the industry, and include, for example, other water-soluble polymers, such as polyethylene oxide (POLYOX™), polyethylene glycol, or polyvinylpyrrolidone (PVP K90).

Polycarbophil is the water insoluble polymer, and provides the extended bioadhesion. Alternatives would include, for example, other water-insoluble, water-swellable bioadhesive polymers.

Table 1 depicts nine different formulations of bioadhesive tablets according to the invention. The active ingredient, testosterone, was held constant at 30.0 mg (24% by weight) so the effect of varying the proportions of the inactive ingredients could be studied.

The testosterone dissolution rates of selected formulations were then studied. Table 2 depicts the testosterone dissolution rate of six tablets selected from Formula 1, batch #0069904. Table 3 depicts the testosterone dissolution rate of six tablets selected from Formula 3, batch #0049904. Table 4 depicts the testosterone dissolution rate of six tablets selected from Formula 5, batch #0029904. Table 5 depicts the testosterone dissolution rate of Formula 6, batch #0019904.

The dissolution rate data was then graphed to illustrate the percent of testosterone released per hour. Chart 1 depicts the testosterone release rate for Formula 1 (see Table 2). Chart 2 depicts the testosterone release rate for Formula 3 (see Table 3). Chart 3 depicts the testosterone release rate for Formula 5 (see Table 4). Chart 4 depicts the testosterone release rate for Formula 6 (see Table 5).

TABLE 1

Testosterone KT										
	Form. 1		Form. 2		Form. 3 Batch #		Form. 4		Form. 5	
	0069904		0059904		0049904		0039904		0029904	
	mg	% by Weight	mg	% by Weight	mg	% by Weight	mg	% by Weight	mg	% by Weight
Testosterone	30.000	24.00	30.000	24.00	30.000	24.00	30.000	24.00	30.000	24.00
HPMC* 90SH-15000	31.250	25.00	30.000	24.00	28.750	23.00	27.500	22.00	26.250	21.00
Cornstarch	2.500	2.00	7.500	6.00	12.500	10.00	17.500	14.00	22.500	18.00
Monohydrated lactose	11.375	9.10	13.875	11.10	16.375	13.10	18.875	15.10	21.375	17.10
Silica	1.250	1.00	1.250	1.00	1.250	1.00	1.250	1.00	1.250	1.00
Polycarbophil acid (Noveon AA-)	3.125	2.50	3.125	2.50	3.125	2.50	3.125	2.50	3.125	2.50
Carbomer 974 P	43.750	35.00	37.500	30.00	31.250	25.00	25.000	20.00	18.750	15.00
Talc	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70
Magnesium sterate	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70
Total Weight	125.000	100.00	125.000	100.00	125.000	100.00	125.000	100.00	125.000	100.00

	Form. 6		Form. 7		Form. 8		Form. 9	
	Batch #							
	0019904		00019906		00029906		00039906	
	mg	% by Weight	mg	% by Weight	mg	% by Weight	mg	% by Weight
Testosterone	30.000	24.00	30.000	24.00	30.000	24.00	30.000	24.00
HPMC* 90SH-15000	26.250	21.00	26.250	21.00	26.250	21.00	26.250	21.00
Cornstarch	22.500	18.00	22.500	18.00	22.500	18.00	22.500	18.00
Monohydrated lactose	24.500	19.60	27.625	22.10	30.125	24.10	33.250	26.60
Silica	1.250	1.00	1.250	1.00	1.250	1.00	1.250	1.00
Polycarbophil acid (Noveon AA-)	3.125	2.50	3.125	2.50	3.125	2.50	3.125	2.50
Carbomer 974 P	15.625	12.50	12.500	10.00	9.375	7.50	6.250	5.00

TABLE 1-continued

	Testosterone KT							
Talc	0.875	0.70	0.875	0.70	1.500	1.20	1.500	1.20
Magnesium sterate	0.875	0.70	0.875	0.70	0.875	0.70	0.875	0.70
Total Weight	125.000	100.00	125.000	100.00	125.000	100.00	125.000	100.00

*Hydroxypropylmethyl cellulose

TABLE 2

TESTOSTERONE DISSOLUTION RATE - PERCENT DISSOLUTION
BATCH: 0069904 (Formula 1)
DISSOLUTION APPARATUS: ROTATING PADDLE 60 RPM/PLATINUM WIRE SPIRAL

SAMPLE	WITHDRAW (HOUR) 0	WITHDRAW (HOUR) 1	WITHDRAW (HOUR) 2	WITHDRAW (HOUR) 4	WITHDRAW (HOUR) 6	WITHDRAW (HOUR) 8	WITHDRAW (HOUR) 24
1	0.0	0.7	1.9	7.6	10.6	16.0	83.6
2	0.0	0.6	1.7	6.7	11.7	18.0	88.5
3	0.0	0.7	2.0	6.9	11.7	17.9	84.9
4	0.0	0.6	1.7	7.0	11.2	17.1	88.3
5	0.0	0.7	1.9	6.8	10.9	17.0	87.4
6	0.0	0.7	2.1	6.6	12.4	18.3	86.6
AVERAGE VALUE	0.0	0.7	1.9	6.9	11.4	17.4	86.6

TABLE 3

TESTOSTERONE DISSOLUTION RATE - PERCENT DISSOLUTION
BATCH: 0049904 (Formula 3)
DISSOLUTION APPARATUS: ROTATING PADDLE 60 RPM/PLATINUM WIRE SPIRAL

SAMPLE	WITHDRAW (HOUR) 0	WITHDRAW (HOUR) 1	WITHDRAW (HOUR) 2	WITHDRAW (HOUR) 4	WITHDRAW (HOUR) 6	WITHDRAW (HOUR) 8	WITHDRAW (HOUR) 24
1	0.0	0.9	3.1	5.6	10.6	16.5	83.6
2	0.0	1.1	3.1	5.6	10.5	16.9	82.2
3	0.0	1.2	3.4	6.3	11.8	18.0	83.4
4	0.0	0.9	2.9	5.4	10.8	16.7	82.7
5	0.0	1.1	4.9	5.7	10.6	16.7	83.0
6	0.0	1.0	2.9	5.6	11.0	16.8	85.6
AVERAGE VALUE	0.0	1.0	3.4	5.7	10.9	16.9	83.4

TABLE 4

TESTOSTERONE DISSOLUTION RATE - PERCENT DISSOLUTION
BATCH: 0029904 (Formula 5)
DISSOLUTION APPARATUS: ROTATING PADDLE 60 RPM/PLATINUM WIRE SPIRAL

SAMPLE	WITHDRAW (HOUR) 0	WITHDRAW (HOUR) 1	WITHDRAW (HOUR) 2	WITHDRAW (HOUR) 4	WITHDRAW (HOUR) 6	WITHDRAW (HOUR) 8	WITHDRAW (HOUR) 24
1	0.0	0.9	2.2	5.9	10.8	16.3	80.3
2	0.0	0.9	2.5	6.7	11.8	17.8	87.5
3	0.0	0.9	2.4	6.9	12.3	17.7	75.2
4	0.0	0.9	2.3	6.8	12.4	18.6	82.4
5	0.0	0.9	2.5	6.9	12.9	19.5	83.2
6	0.0	0.9	2.2	6.6	12.2	18.8	86.6
AVERAGE VALUE	0.0	0.9	2.4	6.6	12.1	18.1	82.5

TABLE 5

TESTOSTERONE DISSOLUTION RATE - PERCENT DISSOLUTION
BATCH: 0019904 (Formula 6)
DISSOLUTION APPARATUS: ROTATING PADDLE 60 RPM/PLATINUM WIRE SPIRAL

SAMPLE	WITHDRAW (HOUR) 0	WITHDRAW (HOUR) 1	WITHDRAW (HOUR) 2	WITHDRAW (HOUR) 4	WITHDRAW (HOUR) 6	WITHDRAW (HOUR) 8	WITHDRAW (HOUR) 24
1	0.0	1.2	2.1	5.9	11.1	16.1	71.7
2	0.0	0.8	2.0	5.0	9.7	14.1	70.1
3	0.0	0.9	2.3	6.4	11.3	15.8	74.6
4	0.0	0.9	2.0	5.5	10.4	15.0	68.6
5	0.0	0.8	1.8	4.9	9.9	14.6	76.6
6	0.0	0.9	1.8	4.9	9.1	13.1	70.3
AVERAGE VALUE	0.0	0.9	2.0	5.4	10.3	14.8	72.0

As shown in the charts and tables, by decreasing the amount of lactose and corn starch and increasing the amount of water-soluble polymer, the time it takes for the tablet to hydrate is progressively decreased. Formulation 1 (0069904) and others like it with high levels of carbomer 974P and low levels of lactose and corn starch are probably best suited to buccal administration where 12 hours of delivery is usually sufficient. In the first example given above Formulation 8 (0029906), where the levels of lactose and corn starch are high and carbomer 974P is low, the formula is probably better suited for vaginal administration where release is often required over a period of days.

Example 2

Testosterone Tablet (30 mg)

The following is an example of a formulation designed for testosterone replacement therapy:

INGREDIENT	AMOUNT/tablet	% w/w
Testosterone	30.000 mg	21.4%
HPMC	26.250 mg	18.8%
Corn Starch	22.500 mg	16.1%
Lactose	45.125 mg	32.2%
Silica	1.250 mg	0.9%
Polycarbophil (Noveon)	3.125 mg	2.2%
Carbomer 974P	9.375 mg	6.7%
Talc	1.500 mg	1.1%
Magnesium stearate	0.875 mg	0.6%

Example 3

Testosterone Tablet (6 mg)

The following is an example of a formulation designed for testosterone replacement therapy:

INGREDIENT	AMOUNT/tablet	% w/w
Testosterone	6.000 mg	6.0%
HPMC	5.250 mg	5.3%
Corn Starch	4.500 mg	4.5%
Lactose	78.970 mg	79.0%
Silica	0.700 mg	0.7%
Polycarbophil (Noveon)	2.230 mg	2.2%
Carbomer 974P	1.000 mg	1.0%
Talc	0.850 mg	0.9%
Magnesium stearate	0.500 mg	0.5%

Example 4

Testosterone Tablet (3 mg)

The following is an example of a formulation designed for testosterone replacement therapy:

INGREDIENT	AMOUNT/tablet	% w/w
Testosterone	3.000 mg	3.0%
HPMC	2.625 mg	2.6%
Corn Starch	2.250 mg	2.3%
Lactose	86.845 mg	86.8%
Silica	0.700 mg	0.7%
Polycarbophil (Noveon)	2.230 mg	2.2%
Carbomer 974P	1.000 mg	1.0%
Talc	0.850 mg	0.9%
Magnesium stearate	0.500 mg	0.5%

Testosterone dosage levels as low as 3 mg have been tested on female patients. The 3 mg dosage produced serum levels of about 1-1.5 ng/mL. This is about 3-6 times greater than would typically be desired to supplement women with testosterone. Thus, as the serum levels achieved from testosterone dosing are linear with respect to the dosage in the formulation, doses of around 0.5-1 mg should be sufficient to replace testosterone in women.

In men, it would be desirable to replace testosterone using a formulation that lasts about 16-18 hours. Dosage levels of 30 mg supply physiologic concentrations of testosterone when administered twice daily, i.e., once every 12 hours. Thus, a 16-18 hour formulation would require about 45 mg to supply physiologic testosterone replacement.

Example 5

Terbutaline Tablet (4 mg)

The following is an example of a terbutaline formulation designed to provide certain therapeutic benefits of terbutaline administration:

INGREDIENT	AMOUNT/tablet	% w/w
Terbutaline sulfate	4.000 mg	4.4%
HPMC	18.760 mg	20.8%
Corn Starch	16.070 mg	17.9%
Lactose	39.640 mg	44.1%
Silica	0.900 mg	1.0%
Polycarbophil (Noveon)	2.235 mg	2.5%

-continued

INGREDIENT	AMOUNT/tablet	% w/w
Carbomer 974P	6.700 mg	7.4%
Talc	1.070 mg	1.2%
Magnesium stearate	0.625 mg	0.7%

Example 6

Terbutaline Tablet (2 mg)

The following is an example of a terbutaline formulation designed to provide certain therapeutic benefits of terbutaline administration:

INGREDIENT	AMOUNT/tablet	% w/w
Terbutaline Sulfate	2.000 mg	2.2%
HPMC	18.760 mg	20.8%
Corn Starch	16.070 mg	17.9%
Lactose	41.640 mg	46.3%
Silica	0.900 mg	1.0%
Polycarbophil (Noveon)	2.235 mg	2.5%
Carbomer 974P	6.700 mg	7.4%
Talc	1.070 mg	1.2%
Magnesium stearate	0.625 mg	0.7%

Example 7

Terbutaline Tablet (1 mg)

The following is an example of a terbutaline formulation designed to provide certain therapeutic benefits of terbutaline administration:

INGREDIENT	AMOUNT/tablet	% w/w
Terbutaline Sulfate	1.000 mg	1.1%
HPMC	18.760 mg	20.8%
Corn Starch	16.070 mg	17.9%
Lactose	42640 mg	47.4%
Silica	0.900 mg	1.0%
Polycarbophil (Noveon)	2.235 mg	2.5%
Carbomer 974P	6.700 mg	7.4%
Talc	1.070 mg	1.2%
Magnesium stearate	0.625 mg	0.7%

Example 8

Desmopressin Tablet (0.025 mg)

The following is an example of a desmopressin formulation designed to provide certain therapeutic benefits of desmopressin administration:

INGREDIENT	AMOUNT/tablet	% w/w
Desmopressin Acetate	0.025 mg	0.03%
Magnesium Stearate	1.000 mg	1.00%
Silicon Dioxide	1.000 mg	1.00%
Talc	1.000 mg	1.00%
Hydroxypropylmethylcellulose 5 cps	1.500 mg	1.50%
Polycarbophil (Noveon)	2.235 mg	2.23%
Carbopol 971P	6.700 mg	6.70%
Hydroxypropylmethylcellulose 100,000 cps	20.000 mg	20.00%

-continued

INGREDIENT	AMOUNT/tablet	% w/w
Lactose, anhydrous	32.460 mg	32.46%
Lactose, monohydrate	34.080 mg	34.08%

Example 9

Desmopressin Tablet (0.1 mg)

The following is an example of a desmopressin formulation designed to provide certain therapeutic benefits of desmopressin administration:

INGREDIENT	AMOUNT/tablet	% w/w
Desmopressin Acetate	0.105 mg	0.10%
Magnesium Stearate	1.000 mg	1.00%
Silicon Dioxide	1.000 mg	1.00%
Talc	1.000 mg	1.00%
Hydroxypropylmethylcellulose 5 cps	1.500 mg	1.50%
Polycarbophil (Noveon)	2.235 mg	2.24%
Carbopol 971P	6.700 mg	6.70%
Hydroxypropylmethylcellulose 100,000 cps	20.000 mg	20.00%
Lactose, anhydrous	32.460 mg	32.46%
Lactose, monohydrate	34.000 mg	34.00%

The Plasma desmopressin pharmacokinetic parameters are listed in Table 6. Levels became measurable in 4-6 hours, and were maintained for up to 16 hours. This example demonstrated that delivery of desmopressin could be sustained.

TABLE 6

Plasma Pharmacokinetic Parameters of Example 9

Parameter	Mean (± SD)
C_{max} (pg/mL)	8.4 (12.0)
C_{avg} (pg/mL)	2.7 (4.4)
T_{max} (h)	9.7 (2.7)
$AUC_{(0-24\ h)}$ (pg · h/mL)	65.3 (104.9)
$t_{1/2el}$ (h)	8.6 (7.4)

Example 10

Desmopressin Tablet (0.2 mg)

The following is an example of a desmopressin formulation designed to provide certain therapeutic benefits of desmopressin administration:

INGREDIENT	AMOUNT/tablet	% w/w
Desmopressin Acetate	0.210 mg	0.21%
Magnesium Stearate	1.000 mg	1.00%
Silicon Dioxide	1.000 mg	1.00%
Talc	1.000 mg	1.00%
Hydroxypropylmethylcellulose 5 cps	1.500 mg	1.50%
Polycarbophil (Noveon)	2.235 mg	2.24%
Carbopol 971P	6.700 mg	6.70%
Hydroxypropylmethylcellulose 100,000 cps	20.000 mg	20.00%
Lactose, anhydrous	32.460 mg	32.46%
Lactose, monohydrate	33.895 mg	33.89%

Data on desmopressin suggests that the 0.1 mg and 0.2 mg dosages provide serum concentrations that are linear with respect to dosages administered in a formulation. Some for-

mulations have shown mean serum concentrations of about 60 pg/mL, ranging up to about 100 pg/mL. This concentration is extremely high and needs to be decreased about 4-fold. In addition, the use of this product in children will necessitate the dosage being reduced even further to about 0.025 mg.

Example 11

Desmopressin Tablet (0.2 mg)

The following is an example of a desmopressin formulation designed to provide certain therapeutic benefits of desmopressin administration:

INGREDIENT	AMOUNT/tablet	% w/w
Desmopressin Acetate	0.210 mg	0.21%
Polysorbate 80	0.500 mg	0.50%
Magnesium Stearate	1.000 mg	1.00%
Silicon Dioxide	1.000 mg	1.00%
Talc	1.000 mg	1.00%
Hydroxypropylmethylcellulose 5 cps	1.500 mg	1.50%
Polycarbophil (Noveon)	1.000 mg	1.00%
Sodium Lauryl Sulfate	2.000 mg	2.00%
Carbopol 971P	2.500 mg	2.50%
Lactose, anhydrous	31.790 mg	31.79%
Lactose, monohydrate	57.500 mg	57.50%

Average plasma desmopressin pharmacokinetic parameters are listed in Table 7. After the administration of the sustained release formulations containing polysorbate 80 and sodium lauryl sulfate, the absorption of desmopressin was enhanced with the plasma drug concentration levels over 100 pg/mL) and the onset of action (within 60 to 90 minutes) was delayed relative to the immediate release tablet due to the addition of the polymers. Peak leveled between 4-6 hours before normal pharmacokinetic decline and the duration of action was approximately 16 hours. The tablet disappeared after 4 to 5 hours.

TABLE 7

Plasma Pharmacokinetic Parameters of Example 11

Parameter	Mean (± SD)
C_{max} (pg/mL)	65.7 (45.5)
C_{avg} (pg/mL)	14.3 (11.1)
T_{max} (h)	5.0 (2.1)
$AUC_{(0-24\ h)}$ (pg · h/mL)	342.5 (266.3)
$t_{1/2el}$ (h)	2.0 (0.6)

Example 12

Desmopressin Tablet (0.05 mg)

The following is an example of a desmopressin formulation designed to provide certain therapeutic benefits of desmopressin administration:

INGREDIENT	AMOUNT/tablet	% w/w
Desmopressin Acetate	0.053 mg	0.06%
Polysorbate 80	0.500 mg	0.56%
Magnesium Stearate	1.000 mg	1.11%
Silicon Dioxide	1.000 mg	1.11%
Talc	1.000 mg	1.11%
Hydroxypropylmethylcellulose 5 cps	1.500 mg	1.67%

-continued

INGREDIENT	AMOUNT/tablet	% w/w
Polycarbophil (Noveon)	1.000 mg	1.11%
Sodium Lauryl Sulfate	1.000 mg	1.11%
Carbopol 974P	2.500 mg	2.78%
Cetomacrogol 1000	3.000 mg	3.33%
Lactose, anhydrous	19.800 mg	22.00%
Lactose, monohydrate	57.647 mg	64.05%

Average plasma desmopressin pharmacokinetic parameters are listed in Table 8. Pharmacokinetic parameters (C_{max} and $AUC_{(0-t)}$) indicated systemic exposure. Mean T_{max} is approximately 4 hours.

TABLE 8

Plasma Pharmacokinetic Parameters of Example 12

Parameter	Mean (± SD)
C_{max} (pg/mL)	3.47 (2.72)
T_{max} (h)	4.33 (1.51)
$AUC_{(0-t)}$ (pg · h/mL)	12.09 (12.82)
T_{nq} (h)	8.67 (3.50)

Example 13

Desmopressin Tablet (0.2 mg)

The following is an example of a desmopressin formulation designed to provide certain therapeutic benefits of desmopressin administration:

INGREDIENT	AMOUNT/tablet	% w/w
Desmopressin Acetate	0.210 mg	0.23%
Polysorbate 80	0.500 mg	0.56%
Magnesium Stearate	1.000 mg	1.11%
Silicon Dioxide	1.000 mg	1.11%
Talc	1.000 mg	1.11%
Hydroxypropylmethylcellulose 5 cps	1.500 mg	1.67%
Polycarbophil (Noveon)	1.000 mg	1.11%
Sodium Lauryl Sulfate	1.000 mg	1.11%
Carbopol 974P	2.500 mg	2.78%
Cetomacrogol 1000	3.000 mg	3.33%
Lactose, anhydrous	19.800 mg	22.00%
Lactose, monohydrate	57.490 mg	63.88%

Average plasma desmopressin pharmacokinetic parameters are listed in Table 9. Pharmacokinetic parameters (C_{max} and $AUC_{(0-t)}$) indicated systemic exposure. Mean T_{max} is approximately 4 hours.

TABLE 9

Plasma Pharmacokinetic Parameters of Example 13

Parameter	Mean (± SD)
C_{max} (pg/mL)	14.20 (5.55)
T_{max} (h)	4.00 (1.07)
$AUC_{(0-t)}$ (pg · h/mL)	57.74 (21.73)
T_{nq} (h)	11.01 (1.52)

As dose increased from 50 to 200 μg, C_{max} and $AUC_{(0-t)}$ increased by approximately 2.2 to 4.4 fold for examples 12 and 13.

Example 14

Desmopressin Tablet (0.05 mg)

The following is an example of a desmopressin formulation designed to provide certain therapeutic benefits of desmopressin administration:

INGREDIENT	AMOUNT/tablet	% w/w
Desmopressin Acetate	0.053 mg	0.06%
Polysorbate 80	0.500 mg	0.56%
Magnesium Stearate	1.000 mg	1.11%
Silicon Dioxide	1.000 mg	1.11%
Talc	1.000 mg	1.11%
Hydroxypropylmethylcellulose 5 cps	1.500 mg	1.67%
Polycarbophil (Noveon)	1.000 mg	1.11%
Carbopol 974P	2.500 mg	2.78%
Cetomacrogol 1000	3.000 mg	3.33%
Sodium Citrate	2.000 mg	2.22%
Lactose, anhydrous	18.800 mg	20.89%
Lactose, monohydrate	57.647 mg	64.05%

Average plasma pharmacokinetic parameters are listed in Table 10. Pharmacokinetic parameters (C_{max} and $AUC_{(0\text{-}t)}$ indicated systemic exposure. Mean T_{max} is approximately 4.5 hours.

TABLE 10

Plasma Pharmacokinetic Parameters of Example 14

Parameter	Mean (± SD)
C_{max} (pg/mL)	3.16 (1.59)
T_{max} (h)	4.57 (1.51)
$AUC_{(0-t)}$ (pg · h/mL)	5.55 (7.85)
T_{nq} (h)	6.86 (1.57)

Example 15

Desmopressin Tablet (0.2 mg)

The following is an example of a desmopressin formulation designed to provide certain therapeutic benefits of desmopressin administration:

INGREDIENT	AMOUNT/tablet	% w/w
Desmopressin Acetate	0.210 mg	0.23%
Polysorbate 80	0.500 mg	0.56%
Magnesium Stearate	1.000 mg	1.11%
Silicon Dioxide	1.000 mg	1.11%
Talc	1.000 mg	1.11%
Hydroxypropylmethylcellulose 5 cps	1.500 mg	1.67%
Polycarbophil (Noveon)	1.000 mg	1.11%
Carbopol 974P	2.500 mg	2.78%
Cetomacrogol 1000	3.000 mg	3.33%
Sodium Citrate	2.000 mg	2.22%
Lactose, anhydrous	18.800 mg	20.89%
Lactose, monohydrate	57.490 mg	63.88%

Average plasma desmopressin pharmacokinetic parameters are listed in Table 11. Pharmacokinetic parameters (C_{max} and $AUC_{(0\text{-}t)}$) indicated systemic exposure. Mean T_{max} is approximately 4 hours.

TABLE 11

Plasma Pharmacokinetic Parameters of Example 15

Parameter	Mean (± SD)
C_{max} (pg/mL)	13.30 (11.50)
T_{max} (h)	5.00 (1.07)
$AUC_{(0-t)}$ (pg · h/mL)	60.80 (70.22)
T_{nq} (h)	11.75 (2.49)

As dose increased from 50 to 200 μg, C_{max} and $AUC_{(0\text{-}t)}$ increased by approximately 2.2 to 4.4 fold for examples 14 and 15.

Example 16

Prostaglandin E_2 Tablet (2 mg)

The following is an example of a formulation designed for PGE_2 replacement therapy:

INGREDIENT	AMOUNT/ tablet	% w/w
PGE_2	2 mg	2.0%
HPMC	6.250 mg	6.2%
Corn Starch	5.500 mg	5.5%
Lactose	80.970 mg	81.0%
Silica	0.700 mg	0.7%
Polycarbophil (Noveon)	2.230 mg	2.2%
Carbomer 974P	1.000 mg	1.0%
Talc	0.850 mg	0.9%
Magnesium stearate	0.500 mg	0.5%

Example 17

Prostaglandin E_2 Tablet (1 mg)

The following is an example of a formulation designed for PGE_2 replacement therapy:

INGREDIENT	AMOUNT/ tablet	% w/w
PGE_2	1 mg	1.0%
HPMC	2.625 mg	2.6%
Corn Starch	2.250 mg	2.3%
Lactose	88.845 mg	88.8%
Silica	0.700 mg	0.7%
Polycarbophil (Noveon)	2.230 mg	2.2%
Carbomer 974P	1.000 mg	1.0%
Talc	0.850 mg	0.9%
Magnesium stearate	0.500 mg	0.5%

Example 18

Prostaglandin E_2 Tablet (0.5 mg)

The following is an example of a formulation designed for PGE_2 treatment:

INGREDIENT	AMOUNT/ tablet	% w/w
PGE_2	0.5 mg	0.5%
HPMC	2.875 mg	2.9%

-continued

INGREDIENT	AMOUNT/ tablet	% w/w
Corn Starch	2.50 mg	2.5%
Lactose	88.845 mg	88.8%
Silica	0.700 mg	0.7%
Polycarbophil (Noveon)	2.230 mg	2.2%
Carbomer 974P	1.000 mg	1.0%
Talc	0.850 mg	0.9%
Magnesium stearate	0.500 mg	0.5%

Prostaglandin E_2 tablets preferably include up to about 2 mg per dosage, however more preferably the tablets include up to about 0.5 mg per dosage or less.

Example 19

Metronidazole Tablets (0.043 mg)

The following is an example of a metonidazole formulation designed to provide certain therapeutic benefits of antimicrobial treatment:

INGREDIENT	AMOUNT/ tablet	% w/w
Metronidazole	0.043 mg	0.03%
Hydroxypropyl cellulose (Klucel ® MF)	21.450 mg	15.00%
Carragenan (Seaspan ® PF)	21.450 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	21.450 mg	15.00%
Polycarbophil (Noveon)	3.289 mg	2.30%
Mannitol	71.672 mg	50.12%
Silica	1.144 mg	0.80%
Talc	1.430 mg	1.00%
Magnesium stearate	1.073 mg	0.75%

Progressive hydration tests were conducted on the tablets from this example by soaking five tablets into a blue dye solution and one tablet was removed from the solution at 20 minutes, 1, 2, 4, and 5 hours, respectively. At each timepoint, each tablet was cut in half using a razor blade and a digital picture was taken against a ruler scale. Pictures taken at different timepoints were compared and the progression of hydration was measured on a scale. Tablets from the example above containing 0.03% w/w metronidazole is progressively hydrated upon contact with water over 5 hours. Tablet length was increased from 9.2 mm to 14.5 mm (58% increased).

Adhesion tests were conducted on the tablets from this example by using a tablet hardness tester (Vankel VK 200 or equivalent). The flat side of each tablet was laid down onto approximately 4 μL of deionized water on the middle of the adhesion bracket. The tablet was pressed for one second to allow the water drop to spread under the surface of the tablet before placing the dedicated weight support on the instrument base plate around the tablet and inserting a 100 g weight. After allowing the weight to stand on the tablet for 60 minutes without disturbing, the weight and weight support were carefully removed. The adhesion value was recorded from the force needed to move the tablet in kp. The adhesion values of tablets from this example are ranged from 4 to 6 kp.

Example 20

Metronidazole Tablets (43.2 mg)

The following is an example of a metonidazole formulation designed to provide certain therapeutic benefits of antimicrobial treatment:

INGREDIENT	AMOUNT/ tablet	% w/w
Metronidazole	43.200 mg	30.00%
Hydroxypropyl cellulose (Klucel ® MF)	21.600 mg	15.00%
Carragenan (Seaspan ® PF)	21.600 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	21.600 mg	15.00%
Polycarbophil (Noveon)	3.312 mg	2.30%
Mannitol	29.016 mg	20.15%
Silica	1.152 mg	0.80%
Talc	1.440 mg	1.00%
Magnesium stearate	1.080 mg	0.75%

The tablets from this example containing 30% w/w metronidazole were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 12.5 mm (36% increased). The adhesion values of tablets from this example using a similar method described in Example 19 are ranged from 4 to 6 kp.

Example 21

Metronidazole Tablets (0.043 mg)

The following is an example of a metonidazole formulation designed to provide certain therapeutic benefits of antimicrobial treatment:

INGREDIENT	AMOUNT/ tablet	% w/w
Metronidazole	0.043 mg	0.03%
Hydroxypropyl cellulose (Klucel ® MF)	21.600 mg	15.00%
Sodium Alginate (Protanal ® LF120M)	21.600 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	21.600 mg	15.00%
Polycarbophil (Noveon)	3.312 mg	2.30%
Mannitol	72.173 mg	50.12%
Silica	1.152 mg	0.80%
Talc	1.440 mg	1.00%
Magnesium stearate	1.080 mg	0.75%

Tablets from this example containing 0.03% w/w metronidazole were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 16.2 mm (76% increased). The adhesion values of tablets from this example using a similar method described in Example 19 are ranged from 3 to 5.5 kp.

Example 22

Metronidazole Tablets (43.5 mg)

The following is an example of a metonidazole formulation designed to provide certain therapeutic benefits of antimicrobial treatment:

INGREDIENT	AMOUNT/ tablet	% w/w
Metronidazole	43.500 mg	30.00%
Hydroxypropyl cellulose (Klucel ® MF)	21.750 mg	15.00%
Sodium Alginate (Protanal ® LF120M)	21.750 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	21.750 mg	15.00%
Polycarbophil (Noveon)	3.335 mg	2.30%
Mannitol	29.218 mg	20.15%
Silica	1.160 mg	0.80%
Talc	1.450 mg	1.00%
Magnesium stearate	1.088 mg	0.75%

Tablets from this example containing 30% w/w metronidazole were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 18.0 mm (96% increased). The adhesion values of tablets from this example using a similar method described in Example 19 are ranged from 4 to 6 kp.

In vitro dissolution of tablets from this example was conducted using USP Apparatus II (paddle) at 50 rpm in 1000 mL of 0.1 N HCl medium and in 1000 mL of 0.1 NHCl/0.2 Na_3PO_4 buffer pH 7.4.

In acidic medium, 45% metronidazole was released from the tablet in this example within one hour and completely released within 4-hour periods (>90%). In basic medium (pH 7.4 buffer), amount of metronidazole released from the tablet in this example is slower than the amount released in acid medium (20% drug released within one hour) and the release was prolonged up to 12 hours.

Example 23

Metronidazole Tablets (43.2 mg)

The following is an example of a metonidazole formulation designed to provide certain therapeutic benefits of antimicrobial treatment:

INGREDIENT	AMOUNT/ tablet	% w/w
Metronidazole	43.500 mg	30.00%
Hydroxypropyl cellulose (Klucel ® MF)	21.750 mg	15.00%
Carragenan (Seaspan ® PF)	21.750 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	21.750 mg	15.00%
Polycarbophil (Noveon)	3.335 mg	2.30%
Microcrystalline cellulose (Avicel PH105)	29.218 mg	20.15%
Silica	1.160 mg	0.80%
Talc	1.450 mg	1.00%
Magnesium stearate	1.088 mg	0.75%

Tablets from this example containing 30% w/w metronidazole were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 14.9 mm (62% increased). The adhesion values of tablets from this example using a similar method described in Example 19 ranged from 4 to 6 kp.

Example 24

Metronidazole Tablets (42.9 mg)

The following is an example of a metonidazole formulation designed to provide certain therapeutic benefits of antimicrobial treatment:

INGREDIENT	AMOUNT/ tablet	% w/w
Metronidazole	42.900 mg	30.00%
Hydroxypropyl cellulose (Klucel ® MF)	21.450 mg	15.00%
Carragenan (Seaspan ® PF)	21.450 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	21.450 mg	15.00%
Polycarbophil (Noveon)	3.289 mg	2.30%
Calcium phosphate	28.815 mg	20.15%
Silica	1.144 mg	0.80%
Talc	1.430 mg	1.00%
Magnesium stearate	1.073 mg	0.75%

Tablets from this example containing 30% w/w metronidazole were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 14.0 mm (52% increased). The adhesion values of tablets from this example using a similar method described in Example 19 ranged from 3 to 5 kp.

Example 25

Metronidazole Tablets (43.5 mg)

The following is an example of a metonidazole formulation designed to provide certain therapeutic benefits of antimicrobial treatment:

INGREDIENT	AMOUNT/tablet	% w/w
Metronidazole	43.500 mg	30.00%
Carpobol 974P	32.625 mg	22.50%
Polyvinylpyrrolidone (PVP K90)	32.625 mg	22.50%
Polycarbophil (Noveon)	3.335 mg	2.30%
Mannitol	29.218 mg	20.15%
Silica	1.160 mg	0.80%
Talc	1.450 mg	1.00%
Magnesium stearate	1.088 mg	0.75%

Tablets from this example containing 30% w/w metronidazole were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 23.5 mm (155% increased). The adhesion values of tablets from this example using a similar method described in Example 19 ranged from 4 to 6 kp.

Example 26

Ibuprofen Tablets (0.044 mg)

The following is an example of an ibuprofen formulation designed to provide certain therapeutic benefits of pain and inflammation treatment:

INGREDIENT	AMOUNT/tablet	% w/w
Ibuprofen	0.044 mg	0.03%
Hydroxypropyl cellulose (Klucel ® MF)	21.750 mg	15.00%
Carragenan (Seaspan ® PF)	21.750 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	21.750 mg	15.00%
Polycarbophil (Noveon)	3.335 mg	2.30%
Mannitol	72.674 mg	50.12%
Silica	1.160 mg	0.80%
Talc	1.450 mg	1.00%
Magnesium stearate	1.088 mg	0.75%

Tablets from this example containing 0.03% w/w ibuprofen were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 14.0 mm (52% increased). The adhesion values of tablets from this example using a similar method described in Example 19 ranged from 4 to 6 kp.

Example 27

Ibuprofen Tablets (40.5 mg)

The following is an example of an ibuprofen formulation designed to provide certain therapeutic benefits of pain and inflammation treatment:

INGREDIENT	AMOUNT/tablet	% w/w
Ibuprofen	40.500 mg	30.00%
Hydroxypropyl cellulose (Klucel ® MF)	20.250 mg	15.00%
Carragenan (Seaspan ® PF)	20.250 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	20.250 mg	15.00%
Polycarbophil (Noveon)	3.105 mg	2.30%
Mannitol	27.203 mg	20.15%
Silica	1.080 mg	0.80%
Talc	1.350 mg	1.00%
Magnesium stearate	1.013 mg	0.75%

Tablets from this example containing 30% w/w ibuprofen were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 13.2 mm (44% increased). The adhesion values of tablets from this example using a similar method described in Example 19 ranged from 2 to 4 kp.

Example 28

Ibuprofen Tablets (0.043 mg)

The following is an example of an ibuprofen formulation designed to provide certain therapeutic benefits of pain and inflammation treatment:

INGREDIENT	AMOUNT/tablet	% w/w
Ibuprofen	0.043 mg	0.03%
Hydroxypropyl cellulose (Klucel ® MF)	21.600 mg	15.00%
Sodium Alginate (Protanal ® LF120M)	21.600 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	21.600 mg	15.00%
Polycarbophil (Noveon)	3.312 mg	2.30%
Mannitol	72.173 mg	50.12%
Silica	1.152 mg	0.80%
Talc	1.440 mg	1.00%
Magnesium stearate	1.080 mg	0.75%

Tablets from this example containing 0.03% w/w ibuprofen were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 17.8 mm (94% increased). The adhesion values of tablets from this example using a similar method described in Example 19 ranged from 4.5 to 7.5 kp.

Example 29

Ibuprofen Tablets (43.2 mg)

The following is an example of an ibuprofen formulation designed to provide certain therapeutic benefits of pain and inflammation treatment:

INGREDIENT	AMOUNT/tablet	% w/w
Ibuprofen	43.200 mg	30.00%
Hydroxypropyl cellulose (Klucel ® MF)	21.600 mg	15.00%
Carragenan (Seaspan ® PF)	21.600 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	21.600 mg	15.00%
Polycarbophil (Noveon)	3.312 mg	2.30%
Microcrystalline cellulose (Avicel PH105)	29.016 mg	20.15%
Silica	1.152 mg	0.80%
Talc	1.440 mg	1.00%
Magnesium stearate	1.080 mg	0.75%

Tablets from this example containing 30% w/w ibuprofen were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 13.9 mm (51% increased). The adhesion values of tablets from this example using a similar method described in Example 19 ranged from 3.5 to 5.5 kp.

Example 30

Ibuprofen Tablets (42.9 mg)

The following is an example of an ibuprofen formulation designed to provide certain therapeutic benefits of pain and inflammation treatment:

INGREDIENT	AMOUNT/tablet	% w/w
Ibuprofen	43.200 mg	30.00%
Hydroxypropyl cellulose (Klucel ® MF)	21.600 mg	15.00%
Carragenan (Seaspan ® PF)	21.600 mg	15.00%
Polyethylene Oxide (POLYOX ™ WSR-301)	21.450 mg	15.00%
Polycarbophil (Noveon)	3.212 mg	2.30%
Calcium phosphate	29.016 mg	20.15%
Silica	1.152 mg	0.80%
Talc	1.440 mg	1.00%
Magnesium stearate	1.080 mg	0.75%

Tablets from this example containing 30% w/w ibuprofen were progressively hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 13.7 mm (49% increased). The adhesion values of tablets from this example using a similar method described in Example 19 ranged from 2 to 4 kp.

Example 31

Ibuprofen Tablets (42 mg)

The following is an example of an ibuprofen formulation designed to provide certain therapeutic benefits of pain and inflammation treatment:

INGREDIENT	AMOUNT/tablet	% w/w
Ibuprofen	42.000 mg	30.00%
Carpobol 974P	31.500 mg	22.50%
Polyvinylpyrrolidone (PVP K90)	31.500 mg	22.50%
Polycarbophil (Noveon)	3.220 mg	2.30%
Mannitol	28.210 mg	20.15%
Silica	1.120 mg	0.80%
Talc	1.400 mg	1.00%
Magnesium stearate	1.050 mg	0.75%

Tablets from this example containing 30% w/w ibuprofen were progressively by hydrated upon contact with water over 5 hours using a similar method described in Example 19. Tablet length was increased from 9.2 mm to 15.2 mm (65% increased). The adhesion values of tablets from this example using a similar method described in Example 19 are ranged from 4 to 6 kp.

In vitro dissolution of tablets from this example was conducted using USP Apparatus II (paddle) at 50 rpm in 1000 mL of 0.1 N HCl/0.2 M Na_3PO_4 buffer pH 7.4. The amount of ibuprofen release in pH 7.4 buffer at 37° C. from the tablet in this example was sustained for at least 16 hours.

As will be appreciated by one of ordinary skill in the art, the examples and preferred embodiments are not intended to be limiting, and the invention applies to tablets comprised of any active ingredient and any combination of tablet materials. Furthermore, as will be appreciated by one of ordinary skill in the art, the invention is intended to cover the methods of manufacturing and therapeutic uses of the aforementioned tablets.

The invention being thus described, it will be apparent to those skilled in the art that the same may be varied in many ways without departing from the spirit and scope of the invention. Such variations are included within the scope of the appended claims.

All publications and patents or applications mentioned in this specification are certain incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference.

What is claimed is:

1. A bioadhesive controlled, sustained release progressive hydration pharmaceutical composition for delivering an active ingredient to a mucosal surface of a mammal, comprising:

an effective amount of a dry reservoir of an active ingredient, and

a sustained release active ingredient delivery system comprising a bioadhesive water insoluble, water-swellable cross-linked polycarboxylic polymer present in the delivery system in a non-salt form, and a bioadhesive water soluble polymer, wherein the polymers are present in amounts which enable the composition to become progressively hydrated to provide extended release of the active ingredient over time;

wherein the delivery system includes amounts of the polymers which are effective to allow the composition to adhere when contacting a mucosal surface of a mammal for a time sufficient to provide extended release of the active ingredient to the mucosal surface.

2. The composition of claim **1**, wherein the composition is formulated as a tablet for delivery of the active ingredient via the mucosal surface of a buccal, vaginal, nasal, or rectal cavity.

3. The composition of claim **2**, wherein the water insoluble, water-swellable cross-linked polycarboxylic polymer is polycarbophil.

4. The composition of claim **3**, wherein the composition is in the form of a tablet that is formulated to gelify or swell to avoid asphyxiation.

5. The composition of claim **3**, wherein the water soluble polymer is carbomer 974P.

6. The composition of claim **1**, wherein the active ingredient comprises one or more of non-steroidal anti-inflammatory drugs (NSAIDS), anti-infectives, anesthetics, immune system modifiers, muscarinic agonists, muscarinic antagonists, anti-neoplastic agents, vitamin K, ondansetron, levocarnitine, anti-fungals, carbamide peroxide, dopamine antagonists, biphosphonates, nicotine, anti-virals, anti-diabetagenics, peptides, insulin, anti-parkinson agents, low molecular weight heparins, or antimicrobials.

7. The composition of claim **1**, wherein the active ingredient comprises one or more of follicle-stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (HCG), thyroid-stimulating hormone (TSH), tamoxifen, mifepristone, raloxifene, nitroglycerin, isosorbide, erythrityl tetranitrate, pentaerythritol tetranitrate, terbutaline, albuterol, pirbuterol, bitolterol, ritodrine, propranolol, metoprolol, nadolol, atenolol, timolol, esmolol, pindolol, acebutolol, labetalol, morphine, hydromorphone, oxymorphone, codeine, hydrocodone, oxycodone, levorphanol, levallorphan, buprenorphine, fentanyl, nalbuphine, butorphanol, pentazocine, naloxone, nalmefene, diclofenac, etodolac, fenoprofen, lurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxin, oxaprozin, piroxicam, sulindac, tolmetin, lidocaine, cocaine, chloroprocaine, tetracaine, prilocalne, mepivacaine, buipivacaine, levobupivacaine, articaine, ropivacaine, phenol, benzocaine, pramoxine, dyclonine, etidocaine, procaine, proparacaine, dibucaine, pramoxine, misoprostol, imiquimod, bethanecol, oxybutynin, melphalan, fluorouracil, vinca alkaloids, bleomycin, cisplatin, bromocriptine, acyclovir, metformin, octreotide, desmopressin, GNRH, levodopa, or metronidazole.

8. The composition of claim **1**, wherein the active ingredient comprises one or more of estradiol, testosterone, progesterone, terbutaline, prostaglandin E2, desmopressin, metronidazole, or ibuprofen.

9. The composition of claim **8**, wherein the active ingredient comprises testosterone and is present in an amount of about 0.04 mg to 45 mg per unit dosage of the composition.

10. The composition of claim **1**, wherein the delivery system releases the active ingredient for a period of time longer than the immediate release dosage form of the active ingredient.

11. A method for sustained release delivery of an active ingredient to the bloodstream of a mammal through a mucosal surface which comprises administering to a mucosal surface of a mammal in need of receiving the active ingredient a composition that includes an effective amount of a dry reservoir of the active ingredient and a sustained release active ingredient delivery system comprising a bioadhesive water insoluble, water-swellable cross-linked polycarboxylic polymer in a non-salt form, and a bioadhesive water soluble polymer, wherein the delivery system includes amounts of the polymers which are effective to allow the composition to adhere and progressively hydrate when contacting the mucosal surface of a mammal for a time sufficient to provide extended release of the active ingredient to the mucosal surface.

12. The method of claim **11**, wherein the administration is via the mucosal surface of a buccal, vaginal, nasal, or rectal cavity of the mammal.

13. The method of claim **12**, wherein the water insoluble, water-swellable cross-linked polycarboxylic polymer is polycarbophil.

14. The method of claim **13**, wherein the composition is in the form of a tablet is formulated to gelify or swell to avoid asphyxiation.

15. The method of claim **13**, wherein the water soluble polymer is carbomer 974P.

16. The method of claim **11**, wherein the active ingredient comprises one or more of non-steroidal anti-inflammatory drugs (NSAIDS), anti-infectives, anesthetics, immune system modifiers, muscarinic agonists, muscarinic antagonists, anti-neoplastic agents, vitamin K, ondansetron, levocarnitine, anti-fungals, carbamide peroxide, dopamine antagonists, biphosphonates, nicotine, anti-virals, anti-diabetagenics, peptides, insulin, anti-parkinson agents, low molecular weight heparins, or antimicrobials.

17. The method of claim **11**, wherein the active ingredient comprises one or more of follicle-stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (HCG), thyroid-stimulating hormone (TSH), tamoxifen, mifepristone, raloxifene, nitroglycerin, isosorbide, erythrityl tetranitrate, pentaerythritol tetranitrate, terbutaline, albuterol, pirbuterol, bitolterol, ritodrine, propranolol, meto-

prolol, nadolol, atenolol, timolol, esmolol, pindolol, acebutolol, labetalol, morphine, hydromorphone, oxymorphone, codeine, hydrocodone, oxycodone, levorphanol, levallorphan, buprenorphine, fentanyl, nalbuphine, butorphanol, pentazocine, naloxone, nalmefene, diclofenac, etodolac, fenoprofen, lurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxin, oxaprozin, piroxicam, sulindac, tolmetin, lidocaine, cocaine, chloroprocaine, tetracaine, prilocalne, mepivacaine, buipivacaine, levobupivacaine, articaine, ropivacaine, phenol, benzocaine, pramoxine, dyclonine, etidocaine, procaine, proparacaine, dibucaine, pramoxine, misoprostol, imiquimod, bethanecol, oxybutynin, melphalan, fluorouracil, vinca alkaloids, bleomycin, cisplatin, bromocriptine, acyclovir, metformin, octreotide, desmopressin, GNRH, levodopa, or metronidazole.

18. The method of claim **11**, wherein the active ingredient comprises one or more of estradiol, testosterone, progesterone, terbutaline, prostaglandin E2, desmopressin, metronidazole, or ibuprofen.

19. The method of claim **18**, wherein the active ingredient comprises testosterone and is present in an amount of about 0.04 mg to 45 mg per unit dosage of the composition.

20. The method of claim **11**, wherein the delivery system releases the active ingredient for a period of time longer than the immediate release dosage form of the active ingredient.

21. A method of treating a health condition in a human which comprises administering a tablet to a mucosal surface of the human, wherein the tablet progressively hydrates to release an active ingredient over an extended period of time, the tablet comprising an effective amount of a dry reservoir of the active ingredient, and a sustained release active ingredient delivery system comprising a bioadhesive water insoluble, water-swellable cross-linked polycarboxylic polymer present in a non-salt form, and a bioadhesive water soluble polymer, wherein the delivery system includes amounts of the polymers which are effective to allow the composition to adhere and to progressively hydrate when contacting a mucosal surface of a mammal to provide extended release of the active ingredient to the human.

22. The method of claim **21**, wherein the administration is via the mucosal surfaces in a buccal, vaginal, nasal, or rectal cavity of the human.

23. The method of claim **22**, wherein the water insoluble, water-swellable cross-linked polycarboxylic polymer is polycarbophil.

24. The method of claim **23**, wherein the composition is in the form of a tablet is formulated to gelify or swell to avoid asphyxiation.

25. The method of claim **23**, wherein the water soluble polymer is carbomer 974P.

26. The method of claim **21**, wherein the active ingredient comprises one or more of non-steroidal anti-inflammatory drugs (NSAIDS), anti-infectives, anesthetics, immune system modifiers, muscarinic agonists, muscarinic antagonists, anti-neoplastic agents, vitamin K, ondansetron, levocarnitine, anti-fungals, carbamide peroxide, dopamine antagonists, biphosphonates, nicotine, anti-virals, anti-diabetagenics, peptides, insulin, anti-parkinson agents, low molecular weight heparins, or antimicrobials.

27. The method of claim **21**, wherein the active ingredient comprises one or more of follicle-stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (HCG), thyroid-stimulating hormone (TSH), tamoxifen, mifepristone, raloxifene, nitroglycerin, isosorbide, erythrityl tetranitrate, pentaerythritol tetranitrate, terbutaline, albuterol, pirbuterol, bitolterol, ritodrine, propranolol, metoprolol, nadolol, atenolol, timolol, esmolol, pindolol, acebutolol, labetalol, morphine, hydromorphone, oxymorphone, codeine, hydrocodone, oxycodone, levorphanol, levallorphan, buprenorphine, fentanyl, nalbuphine, butorphanol, pentazocine, naloxone, nalmefene, diclofenac, etodolac, fenoprofen, lurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxin, oxaprozin, piroxicam, sulindac, tolmetin, lidocaine, cocaine, chloroprocaine, tetracaine, prilocalne, mepivacaine, buipivacaine, levobupivacaine, articaine, ropivacaine, phenol, benzocaine, pramoxine, dyclonine, etidocaine, procaine, proparacaine, dibucaine, pramoxine, misoprostol, imiquimod, bethanecol, oxybutynin, melphalan, fluorouracil, vinca alkaloids, bleomycin, cisplatin, bromocriptine, acyclovir, metformin, octreotide, desmopressin, GNRH, levodopa, or metronidazole.

28. The method of claim **21**, wherein the active ingredient comprises one or more of estradiol, testosterone, progesterone, terbutaline, prostaglandin E2, desmopressin, metronidazole, or ibuprofen.

29. The method of claim **21**, wherein the delivery system releases the active ingredient for a period of time longer than the immediate release dosage form of the active ingredient.

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